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Neurology

Ependymoma of the Brain: Pathologic Aspects

Hendrik J. Svien, M.D., Robert F. Mabon, M.D., James W. Kernohan, M.D. and Winchell McK. Craig, M.D.

STORCH[1] is credited by Scherer as being the first to describe clearly, in 1899, a brain tumor whose general structure differed from that of both the main groups known until then, glioma and sarcoma. In a child aged six years he found a partially cystic tumor of the parietal lobe characterized by a curious papillary perivascular structure, its cells forming "crowns of rays" around the vessels, and in other places he noted tubular structures with a lumen resembling the central canal of the nervous system. There is little doubt that what Storch described is what we call "ependymoma" today. He even described dark corpuscles in the cytoplasm of the tumor cells, which in all probability correspond to the "blepharoplasts" considered by Mallory[2] as very important for the diagnosis.

The literature prior to 1924 contains numerous reports of tumors classified as "ependymal gliomas." Bailey,[3] in 1924, analyzed critically the reports of tumors in this varied group and identified only five cases which he could accept as cases of true ependymomas, that is, tumors originating from ependymal cells. The next year he[4] divided the tumors of this group into ependymomas and ependymoblastomas on a histogenetic basis. This subdivision has been used by most neuropathologists since.

In 1931, Kernohan, Woltman and Adson[5] divided the ependymomas, on histologic and architectural grounds, into epithelial, myxopapillary and cellular

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types. Later, in 1937, Kernohan and Fletcher-Kernohan[6] included a fourth variety, namely, papilloma of the choroid plexus. These authors also used the term "ependymoblastoma" for the tumors of ependymal origin, which they considered to be more malignant lesions.

TABLE 1

CORRELATION OF GRADE OF MALIGNANCY OF EPENDYMOMAS WITH THREE-YEAR SURVIVAL RATE

Malignancy grade	*Average postoperative survival, months**	*Three-year survival rate, per cent*
1	77.0	79.3
2	37.7	28.6
3	18.2	11.1
4	10.1	9.1

*Since some of these patients were living at the time of this study, these figures represent minimal estimates of the average postoperative survival.

The most recent advance in the study of the ependymoma group of tumors has been the application of the concept of anaplasia, rather than that of histogenesis, and the grading of the malignancy of these tumors according to the degree of anaplastic change, as reported by Mabon, Svien, Kernohan and Craig.[7] These authors graded the malignancy of these tumors from 1 to 4 on purely histologic grounds and then correlated the grade of malignancy with the postoperative survival period (table 1).

The term "ependymoblastoma" has thus been eliminated from these authors' classification of gliomas.

MICROSCOPIC APPEARANCE

The normal ependymal cell, from which ependymomas are derived, is a polyhedral carrot-shaped cell which has a moderate amount of cytoplasm, with the nucleus situated near the large end and a long trailing process at the other. The presence of "blepharoplasten," which are tiny granules in the cells of ependymomas, has been emphasized by Mallory as a distinguishing feature of ependymomas in contrast to other glial tumors. Bailey,[8] however, found that blepharoplasten might also be present in some pineal and subependymal cells and hence could not be regarded as specific for ependymomas. Kernohan and Fletcher-Kernohan[6] found that many of the ependymomas in their series lacked these granules.

The type cell of ependymoma is about twice the size of an astrocyte. The cells of this tumor are usually fitted tightly together in a mosaic pattern. Not infrequently cells arranged about a clear space, simulating the central canal of the spinal cord, are seen. This formation is known as a "true rosette." Sometimes incomplete rosettes, or "pseudorosettes," are formed. These figures are produced by the pointing of the processes of the cells centrally, thus leaving a more or less clear space or "moose track" free of nuclei. Around

blood vessels the same process is in evidence, with a clear space surrounding the vessel, producing a corona.

Cells morphologically indistinguishable from oligodendroglia are found in about 39 per cent of ependymomas.[6] These may occur as occasional scattered cells or in large concentrated numbers, giving some sections of the tumor an appearance more characteristic of oligodendroglioma than of ependymoma.

Grouping of ependymomas. From the standpoint of cytologic architecture, ependymomas have been divided into four groups by Kernohan and Fletcher-Kernohan,[6] as described in subsequent paragraphs.

1. *Cellular group.* In this group the bulk of the tumor is made up of compact masses of ependymal cells. Pseudorosettes are common. Processes from the cells are few but large. There is frequently a vascular projection but it does not have a well-formed vascular foot. There is rarely more than one process, and it seldom divides. These cells do not have neuroglial fibrils which can be demonstrated with the Mallory phosphotungstic acid hematoxylin stain and they do not become impregnated when Cajal's gold chloride and sublimate method is employed, nor do they react to any of the ordinary silver impregnation methods. Frequently, the cells send their processes toward a common blood vessel, giving a peculiar pseudorosette appearance.

2. *Epithelial group.* Many of the cells grow side by side like cuboidal or columnar epithelium. True rosette and pseudorosette formation is common. There is no basement membrane between the free ends of the cells and the lumina of some of the canals or rosettes. The canals are apparently empty. These cells are not ciliated. Sometimes the rosettes are surrounded by cells which have heavy processes which project into the surrounding tissue. These processes are broad, seldom branch and do not contain neurofibrils. Sometimes the cells of a rosette send processes to a nearby blood vessel, where they become attached to the connective tissue of the wall and in this way simulate a supportive type of astrocyte.

3. *Myxopapillary or papillary group.* The ependymal cells are high cuboidal in type, with a heavy process attached to the core of a papilla. The papillary core is composed of connective tissue which undergoes varying degrees of myxomatous degeneration, resulting in formation of mucus. The mucus is extracellular, and is thought not to be a secretion of the ependymal cell.

4. *Papilloma choroideum group.* These are papillomatous growth and simulate the normal choroid plexus from which they arise. The cells of this type of ependymoma are columnar rather than cuboidal or polyhedral. Many of the cells contain large droplets of mucus.

Except for the papilloma choroideum, the majority of ependymomas contain two, sometime all three types, not only in cell characteristics, but also in their architectural patterns. Only a small number of tumors are made up of just one type.

Grading of ependymomas. When the ependymomas, regardless of architectural type, are considered from the standpoint of anaplasia, they can be divided conveniently into four grades of malignancy, as has been reported by Mabon, Svien, Kernohan and Craig.[7] The criteria for each of the four grades follow:

Grade 1. In this grade, all the cells composing the tumor appear to be normal ependymocytes when stained routinely with hematoxylin and eosin, Mallory-Heidenhain stain, Mallory's phosphotungstic acid hematoxylin or other special stains. The various architectural patterns, such as perivascular actiniform arrangement, pseudorosette formation and papillary patterns, are well formed. There is no evidence of anaplasia as manifested by pleomorphism of the cytoplasm or nucleus, hyperchromatism or the presence of mitotic figures. These tumors, although composed entirely of normal-appearing cells, are considered to be malignant because they are tumefactions located in tissue which is particularly vulnerable to the effects of space-occupying lesions (figures 1, 2 and 3).

Grade 2. In tumors of this group, the architectural pattern is less distinct than that in grade 1 tumors but is readily discernible. The great majority of the component cells are normal-appearing ependymocytes. The remaining cells show evidence of early anaplastic transformation, as manifested by slight to moderate pleomorphism of the cytoplasm and nuclei, and hyperchromatism of the nuclei. No mitotic figures are present (figures 4 and 5).

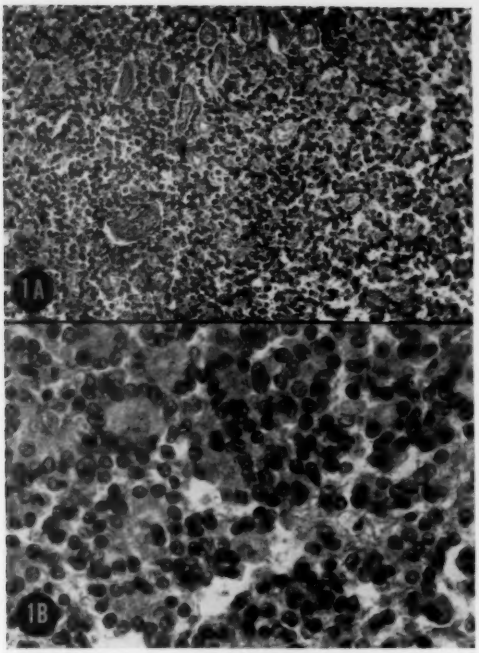
Grade 3. In tumors of this grade, the architectural pattern is still discernible but appears somewhat fragmentary. About one half of the component cells are normal-appearing ependymocytes. The remaining cells show evidence of moderate pleomorphism of the cytoplasm and nuclei, and hyperchromatism of the nuclei. Mitotic figures are present, averaging at least one in every other high-power field (figures 6 and 7).

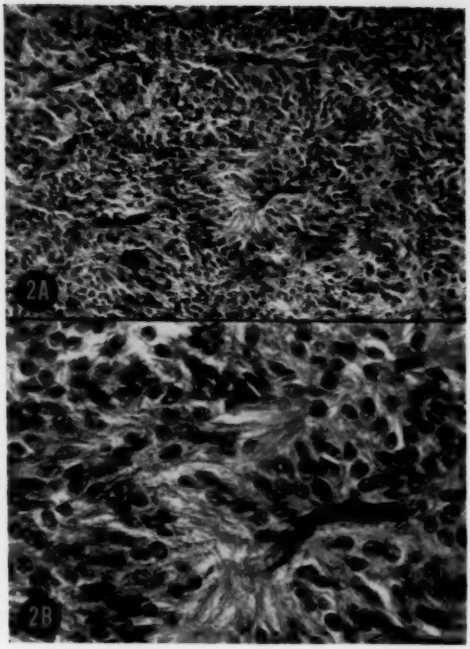
Grade 4. In tumors of this grade, none or only a small number of the cells are normal-appearing ependymocytes. The architectural patterns are presented only as remnants, and the tumor as a whole presents a disorganized picture. The remaining cells show evidence of marked pleomorphism of the cytoplasm and nuclei, and hyperchromatism of the nuclei. Mitotic figures are abundant, averaging 4 or 5 per high-power field (figures 8 and 9).

TABLE 2

RATIO OF EPENDYMOMAS TO ALL GLIOMAS

Author	*Year*	*Ratio, per cent*
Cushing[9]	1932	3.61
List[10]	1936	4.0
Bennett[11]	1946	5.0
Wilson[12]	1940	5.4
Torkildsen[13]	1935	6.7
Baker[14]	1941	8.2
Present authors	1948	9.1





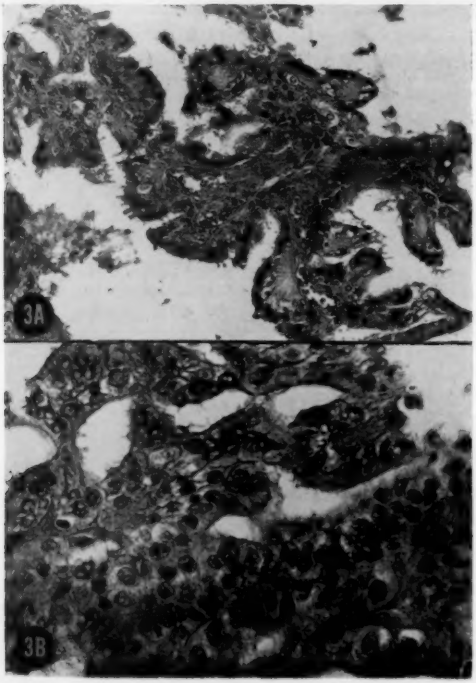


FIG. 1. Epithelial ependymoma, grade 1. *A*. The architectural pattern is distinct. *B*. All the ependymocytes appear to be normal. Evidence of anaplasia is absent.

FIG. 2. Cellular ependymoma, grade 1. *A*. The architectural pattern is distinct. *B*. All the ependymocytes appear to be normal. Evidence of anaplasia is absent.

FIG. 3. Myxopapillary ependymoma, grade 1. *A*. The architectural pattern is distinct. *B*. All the ependymocytes appear to be normal. Evidence of anaplasia is absent. (All hematoxylin and eosin stains).

INCIDENCE

The incidence of ependymomas has been variously reported as being from 3 to 8 per cent of all gliomas (table 2). In the authors' series, 162 of 1,782 gliomas, or 9.1 per cent, were ependymomas. Ependymomas represented 4.8 per cent of total brain tumors in this series. One hundred and twenty-six of the 162 cases of ependymomas were selected as suitable for grading of malignancy. In the cases which were rejected, the diagnosis was established, but tissue suitable for grading of malignancy was not available. This report, then, deals with the 126 cases in which grade of malignancy could be determined.

TABLE 3

DISTRIBUTION OF EPENDYMOMAS ACCORDING TO GRADE OF MALIGNANCY (Entire Group)

Grade	*Ependymomas*	*Per cent*
1	63	50.0
2	17	13.5
3	27	21.4
4	19	15.1
Total	126	100

Grade. The distribution according to grade is given in table 3.

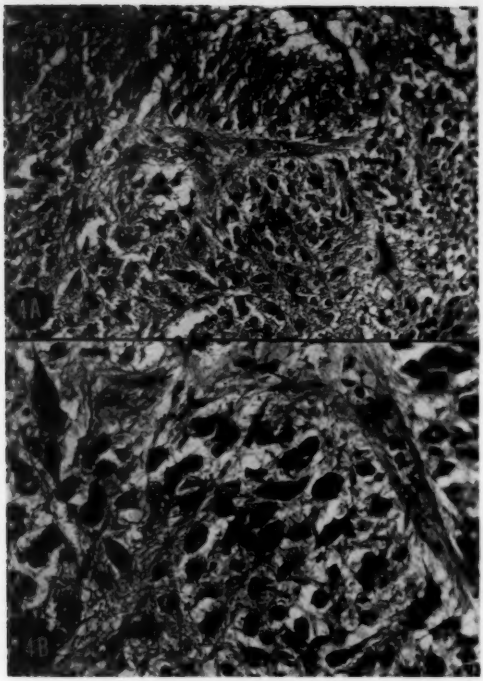
Sex. In Baker's[14] series, eight patients were females, and 16 were males. List,[10] reporting a series of 81 cases of this type of glioma, stated that in the fourth ventricle these tumors are twice as common in the male as in the female, while the cerebral ependymomas do not show a preference for either sex. In our series of 126 cases, 57 (45.2 per cent) occurred in females while 69 (54.8 per cent) occurred in males.

TABLE 4

DISTRIBUTION OF EPENDYMOMAS ACCORDING TO GRADE OF MALIGNANCY AND AGE OF PATIENT (Entire Group)

	Age, years						
Grade	0–9	10–19	20–29	30–39	40–49	50–59	60–69
1	15	15	11	10	8	4	
2	5	1	3	2	6		
3	11	6	3	2	5		
4	6	2	1	1	7	1	1
Total	37	24	18	15	26	5	1

Age. Baker[14] stated that ependymomas are primarily tumors of children. List[10] found that ependymomas of the fourth ventricle attain their maximal incidence between the ages of 10 and 15 years, and have a second peak around 45 years; cerebral ependymomas occurred mostly in late childhood and early adult life with a maximal incidence between the ages of 10 and 25 years, and are rare after the age of 30. Drucker[15] reported a case occurring in a newborn infant. In our series the ages ranged from one to 62 years, the average



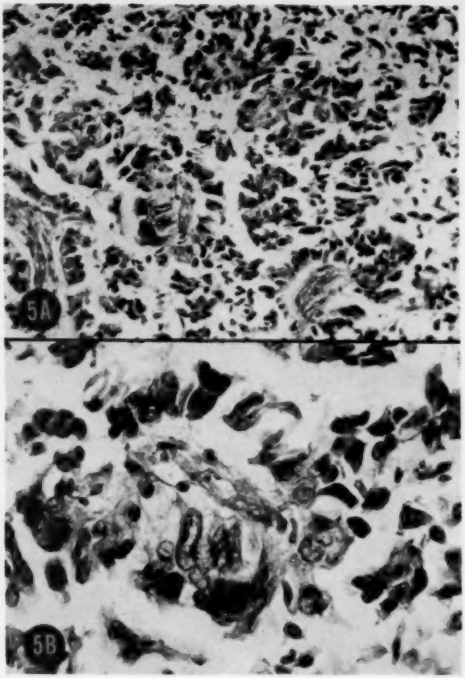


FIG. 4. Cellular ependymoma, grade 2. *A*. The architectural pattern, though still quite definite, shows some disorganization. *B*. Most of the ependymocytes appear to be normal. A few show evidence of early anaplasia, for example, pleomorphism and hyperchromatism of nuclei. No mitotic figures are present.

FIG. 5. Papilloma choroideum ependymoma, grade 2. *A*. The architectural pattern, though still quite distinct, shows some disorganization. *B*. Most of the ependymocytes appear to be normal. A few show evidence of early anaplasia, for example, pleomorphism and hyperchromatism of nuclei. No mitotic figures are present (hematoxylin and eosin stains).

being 23.4 years. The age distribution of patients according to grade of lesion is given in table 4.

Fifty-four (42.9 per cent) of the tumors in this series occurred in the age group 0 to 14 years. The distribution according to grade of malignancy is given in table 5.

TABLE 5

DISTRIBUTION OF EPENDYMOMAS ACCORDING TO GRADE OF MALIGNANCY (Patients 0 to 14 Years Old)

Grade	*Ependymomas*	*Per cent*
1	24	44.4
2	6	11.1
3	16	29.6
4	8	14.8
Total	54	100

LOCATION

In Cushing's series[9] of ependymomas, six of 25 tumors (24 per cent) were

supratentorial, and 19 (76 per cent) were infratentorial. List found that 28 of 81 ependymomas (34.6 per cent) occurred above the tentorium while 53 (65.4 per cent) were present in the posterior fossa.[10] In our series, 51 of 126 ependymomas (40.5 per cent) were supratentorial and 75 (59.5 per cent) were infratentorial. In the age group 0 to 14 years, 21 of 54 ependymomas (38.9 per cent) were supratentorial and 33 (61.1 per cent) were in the posterior fossa.

SUPRATENTORIAL EPENDYMOMAS

Grossly, these tumors are firm, pale to reddish brown in color, partially encapsulated, and occasionally lobulated. They may be 1) entirely intraventricular, 2) partially intraventricular and partially extraventricular, or 3) entirely extraventricular, occurring at varying distances from the ventricular walls. Those in the first two categories take origin from the ventricular ependyma. Of those in the third category, where no connection between the tumor and the ventricular wall can be demonstrated, the theory of ependymal "cell rests" has been used to explain the origin. Such "cell rests" might be the result of a congenital malformation in the infolding of the neural tube. We have frequently encountered such rests of ependymal cells in routine preparations (figure 10).

List[10] has expressed the belief that these tumors preferentially originate at the following sites: 1) at the ends and flexures of the lateral ventricle where ependymal-cell clusters are found in the subependymal layer, 2) near the ventricular outlets, namely, the foramen of Monro and the entrance of the third ventricle into the aqueduct, and 3) at the insertion of the taenia and tela choroidea.

TABLE 6

LOCATION OF 51 SUPRATENTORIAL EPENDYMOMAS

Location	*Side*		*Total*
	Right	*Left*	
Frontal lobe	4	3	7
Frontoparietal region	1	2	3
Frontotemporal region		1	1
Parietal lobe	5	5	10
Parietotemporal region	4		4
Parieto-occipital region	3	1	4
Temporal lobe	3	4	7
Occipital lobe	1	0	1
Hemisphere	2	1	3
Thalamus	2		2
Lateral ventricle		1	1
Third ventricle	8		8
Total	33	18	51

Inasmuch as practically all the supratentorial tumors in our cases were surgical, and only in a few instances did we have the opportunity of studying postmortem specimens, we have not been able to determine the exact bound-

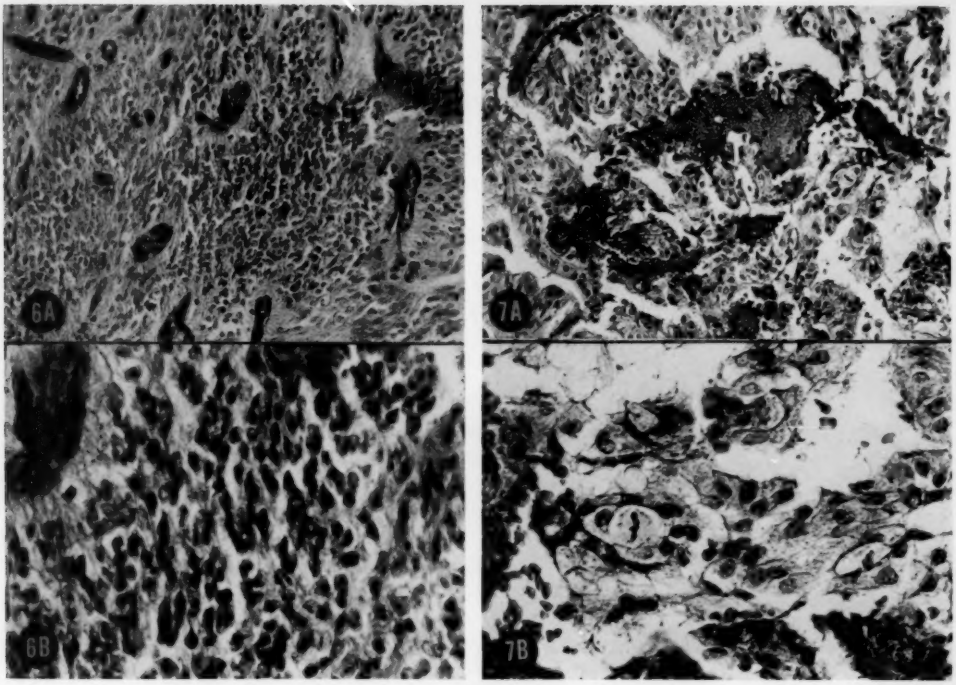


FIG. 6. Cellular ependymoma, grade 3. *A*. The architectural pattern is still discernible, but appears somewhat fragmentary. *B*. About half the ependymocytes appear to be normal. The remaining cells show evidence of anaplasia. Mitotic figures are present, averaging one in every other high-power field.

FIG. 7. Myxopapillary ependymoma, grade 3. *A*. The architectural pattern is still discernible, but appears somewhat fragmentary and disorganized. *B*. About half the ependymocytes appear to be normal. The remaining cells show evidence of anaplasia. Mitotic figures are present, averaging one in every other high-power field (hematoxylin and eosin stains).

aries of the tumors, nor their exact relation to the ventricular walls. The location of these tumors, as determined in the great majority of instances at operation, is given in table 6. It is evident that supratentorial ependymomas show a predilection for the frontal, temporal and parietal lobes, and the third ventricle.

TABLE 7

DISTRIBUTION OF ALL SUPRATENTORIAL EPENDYMOMAS ACCORDING TO GRADE, AND AGE AND SEX OF PATIENTS

Grade	*Number*	*Per cent*	*Average age, years*	*Males*	*Females*
1	17	33.3	24.7	11	6
2	8	15.7	24.9	4	4
3	16	31.4	20.1	8	8
4	10	19.6	30.6	4	6
Total	51	100	25.4	27	24

Of these 51 supratentorial ependymomas, 28 (54.9 per cent) occurred in males, and 23 (45.1 per cent) in females. The ages of the patients ranged from

TABLE 8

DISTRIBUTION OF SUPRATENTORIAL TUMORS OF PATIENTS AGED 0 TO 14 YEARS ACCORDING TO GRADE OF MALIGNANCY

Grade	*Ependymomas*	*Per cent*
1	6	28.6
2	3	14.3
3	9	42.8
4	3	14.3
Total	21	100

one to 62 years, the average being 24.4 years. The distribution of supratentorial ependymomas according to the grade of malignancy, and the average age and the sex of the patients are summarized in table 7.

Twenty-one of the 51 supratentorial tumors (41.2 per cent) were in the age group 0 to 14 years. The distribution according to the grade of malignancy is given in table 8.

The correlation of the grade of supratentorial ependymomas (entire group) with the sex and average age of the patients and with the postoperative survival period is given in table 9.

TABLE 9

CORRELATION OF GRADE OF SUPRATENTORIAL TUMORS (Entire Group) WITH SEX AND AVERAGE AGE OF PATIENTS AND WITH SURVIVAL PERIOD

Grade	*Ratio, males to females*	*Average age, years*	*Patients living at time of survey, per cent*	*Average postoperative survival, months*
1	3:2	27.2	80.0	95.0
2	2:1	27.8	20.0	22.7
3	3:5	23.3	12.5	18.6
4	3:4	32.1	0	3.9

Occurrence of cysts. As has been pointed out by most writers on the subject, supratentorial ependymomas are frequently cystic. In our series, 20 of 51 of these tumors (39.2 per cent) contained cysts. In three cases mural nodules were present. The average age of the patients in whom the tumors were

TABLE 10

DISTRIBUTION OF CYSTIC SUPRATENTORIAL EPENDYMOMAS ACCORDING TO GRADE OF MALIGNANCY

Grade	*Total*	*Cystic*	
		Number	*Per cent*
1	17	8	47.1
2	8	4	50.0
3	16	5	31.3
4	10	3	30.0

cystic was 16.6 years. The size of the cysts varied from 5 to 140 ml. capacity, the average being 66.4 ml. The distribution of the cystic tumors according to grade of malignancy is shown in table 10. It is apparent from this table that

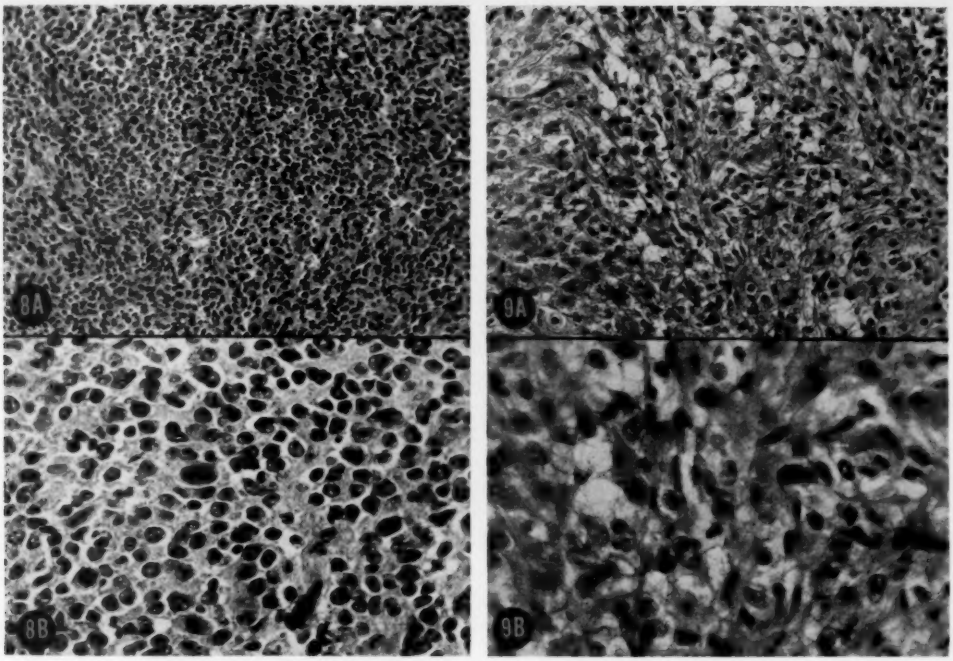


FIG. 8. Epithelial ependymoma, grade 4. *A*. The architectural pattern is present only in fragmentary form, and the tumor as a whole presents a disorganized picture. *B*. Only a few of the ependymocytes appear to be normal. Most of the cells show evidence of anaplasia. Mitotic figures are frequent, averaging four or five per high-power field.

FIG. 9. Cellular ependymoma, grade 4. *A*. The architectural pattern is present only in fragmentary form, and the tumor as a whole presents a disorganized picture. *B*. Most of the ependymocytes show evidence of anaplasia. Mitotic figures are frequent, averaging four or five per high-power field (hematoxylin and eosin stains).

cyst formation is not restricted to tumors of low grade, but occurs in all grades of malignancy.

Calcium deposition. List[10] stated that in his series of 23 cases of supratentorial ependymomas 45 per cent contained calcium deposits that were visible on the roentgenogram. In Fincher and Coon's[16] series, such deposits were visible roentgenographically in three of five cases. In our series calcification was present on microscopic examination in 20 of 51 cases of supratentorial ependymoma (39.2 per cent) (table 11). In nine of these cases of supraten-

TABLE 11

INCIDENCE OF CALCIUM DEPOSITS IN SUPRATENTORIAL EPENDYMOMAS ACCORDING TO GRADE OF MALIGNANCY

		Calcification seen			
		Microscopically		*Roentgenographically*	
Grade	*Total tumors*	*Number*	*Per cent of total in grade*	*Number*	*Per cent of total in grade*
1	17	8	47.1	4	23.5
2	8	1	12.5	0	—
3	16	6	37.5	3	18.8
4	10	5	50.0	2	20.0

torial ependymoma (17.6 per cent) the deposits were evident roentgenographically. Contrary to a commonly held impression that calcium deposition bespeaks benignity in brain tumors, table 11 reveals that calcium deposition occurs in ependymomas of all grades of malignancy.

INFRATENTORIAL EPENDYMOMAS

Infratentorial ependymomas characteristically take origin from the ependymal cells of the floor or the posterior medullary velum of the fourth ventricle. They are usually encapsulated, firm, grayish-colored tumors. They do not infiltrate, except at the site of attachment. At operation they are sometimes completely enclosed within the fourth ventricle, but may grow up between the cerebellar lobes, compressing the roof of the fourth ventricle and the vermis into a thin sheet of tissue overlying them. Very frequently, as has been pointed out by Bailey,[4] these tumors project into the subarachnoid space as a tongue of tissue down through the foramen magnum as far as the midcervical spinal level. Because of their usually small base of attachment and the fact that they are encapsulated, many surgeons consider these tumors enucleable.

Although the great majority of ependymomas of the posterior fossa arise from the ependymal cells lining either the floor or the roof of the fourth ventricle and present as midline tumors, a few of them, as has been pointed out by Kernohan, Woltman and Adson,[5] arise from the ependymal cells of the lateral medullary velum, and grow in the cerebellopontine angle.

TABLE 12

DISTRIBUTION OF INFRATENTORIAL EPENDYMOMAS (Entire Group) ACCORDING TO GRADE OF MALIGNANCY, AND AVERAGE AGE AND SEX OF PATIENTS

Grade	*Number*	*Per cent*	*Average age, years*	*Male*	*Female*
1	45	60.0	22.8	20	25
2	10	13.3	24.6	6	4
3	11	14.7	15.6	6	5
4	9	12.0	24.4	8	1
Total	75	100	22.8	40	35

In our series of 126 intracranial ependymomas, 75 (59.5 per cent) were infratentorial. Of these, 70 (93.3 per cent) presented as midline posterior fossa tumors, and five (6.7 per cent) presented in the cerebellopontine angle.

Of the tumors arising from the floor or roof of the fourth ventricle, 25 (33.3 per cent) had projecting "tongues" which extended in the subarachnoid space through the foramen magnum for varying distances; in one instance the projection extended as far down as the level of the fifth cervical vertebra.

Of the 75 posterior fossa tumors, 40 (53.3 per cent) occurred in males, while 35 (46.7 per cent) occurred in females. The ages of patients with posterior fossa ependymomas ranged from one and a half to 54 years, the average being 22.8 years. The distribution of these tumors according to the grade of malignancy, and the average age and the sex of the patients is given in table 12.

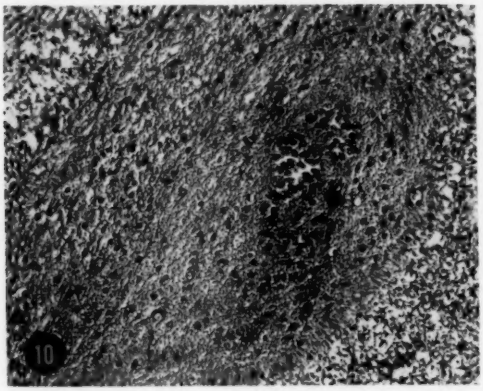


FIG. 10. Ependymal-cell rest. This cluster of cells was found about 1 cm. distal to the tip of the occipital horn of the lateral ventricle.

Thirty-three of the infratentorial ependymomas (44 per cent) were in the age group 0 to 14 years. The distribution according to the grade of malignancy is given in table 13.

TABLE 13

DISTRIBUTION OF INFRATENTORIAL EPENDYMOMAS OF PATIENTS AGED 0 TO 14 YEARS ACCORDING TO GRADE OF MALIGNANCY

Grade	*Ependymomas*	*Per cent*
1	18	54.6
2	3	9.1
3	7	21.1
4	5	15.2
Total	33	100

Cyst formation. Eight of the 75 infratentorial ependymomas (10.7 per cent) were described as being cystic. Of these, seven were grade 1 tumors, and one was a grade 3 tumor. The cysts varied in size up to a capacity of 25 ml. In four cases in which the contents of the cysts were accurately determined, the capacity was, respectively, as follows: 10 ml., 20 ml., 15 ml. and 25 ml. In the remaining cases the tumor was described as cystic without any mention of the size of the cyst.

Calcification. Ependymomas of the posterior fossa have less tendency to calcareous deposition than do the cerebral ependymomas, according to Fincher and Coon.[16] Cushing[9] stated that ependymomas, even when in the posterior fossa, tend to show calcification. However, in a series of seven cases (infratentorial) reported by Bailey, Buchanan and Bucy,[17] no calcium was found.

In our series of ependymomas of the posterior fossa, 19 of 75 (25.3 per cent) showed microscopic deposits of calcium (table 14). This incidence is somewhat less than that which occurred in respect to the supratentorial epen-

TABLE 14

INCIDENCE OF CALCIFICATION IN INFRATENTORIAL EPENDYMOMAS ACCORDING TO GRADE OF TUMOR

Grade	*Total tumors*	*Calcification seen microscopically*	
		Number	*Per cent of total in grade*
1	45	14	31.1
2	10	3	30.0
3	11	1	9.1
4	9	1	11.1

dymomas (39.2 per cent). In no instance of ependymoma of the posterior fossa was calcium evident roentgenographically.

SPINAL SUBARACHNOID IMPLANTATION ASSOCIATED WITH INTRACRANIAL EPENDYMOMA

Spiller[18] in 1907 gave one of the earliest, if not the first, reports of subarachnoid implantation in cases of ependymoma. Implantations in other cases were described by Gordinier and Sawyer[19] in 1911. Cairns and Russell[20] in 1931, Tarlov[21] in 1937, Dyke and Davidoff[22] in 1942, and Tarlov and Davidoff[23] in 1946. Other cases have been reported in the literature as papilloma choroideum with ventricular and spinal implants. Kernohan and Fletcher-Kernohan[6] have suggested that papilloma choroideum is an ependymoma, and we believe that cases reported in the literature as papilloma choroideum with implants should be included. Reports of such cases were collected from the literature by Herren[24] in 1941. He reviewed the data on 88 cases of so-called papilloma choroideum and found that seeding occurred in 20 per cent. When these cases are included with those of ependymoma, the number of cases of ependymoma with implanation is increased.

In 19 of our cases of intracranial ependymoma, the spinal cords were available for study. In six of these cases, or 31.6 per cent, there was implantation in the spinal subarachnoid space. In the 19 cases, seven of the primary intracranial neoplasms occurred above the tentorium, while 12 occurred in the fourth ventricle. It was only in those cases in which the tumor arose in the fourth ventricle that implantation occurred. In all six of our cases in which implantation occurred, a tongue of tumor tissue projected from the fourth ventricle through the cisterna magna into the spinal subarachnoid space at the level of the foramen magnum, and in some instances it protruded as far down as the second cervical segment. In one of our cases in which implantation had taken place, no operation had been done. The grades of malignancy of the tumors associated with implantation were as follows: grade 1, one case; grade 2, one case; grade 3, two cases; and grade 4, two cases.

Although instances have been reported[6] in which the spinal cord implants were proved to account for clinical symptoms and findings, in none of our cases was there clinical evidence of a spinal cord lesion.

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Certain leading facts regarding the structure of the brain must be clearly recognized, if we would understand what is known of the principles of the diagnosis of its diseases. Our present knowledge of the cerebral structure is at once far more than we can use, and far less than we need. . . . . But if we attempt to select from the facts described by different investigators those that are of chief importance, we are at once met by a fresh difficulty. Many of the conclusions reached by different investigators do not correspond – are even contradictory. This is not surprising. The interlacing tracts of fibres baffle the scalpel, and even the microscope, when we attempt to trace their course. What, then, is to be our guide when investigators disagree? Fortunately we are not dependent only on simple dissection, or even microscopical examination. The selective action of disease affords invaluable help in the study of the structure of the nerve-centres.

–Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Tussive Syncope and Its Relation to Epilepsy

Desmond S. O'Doherty, M. D.

TUSSIVE SYNCOPE, known also as laryngeal vertigo or laryngeal epilepsy, is a syndrome in which fainting and vertigo with or without convulsions follows a paroxysm of coughing. It usually occurs in elderly males with pulmonary emphysema and a history of chronic bronchitis. It is the object of this report to prevent five cases and evidence that this syndrome is a type of symptomatic epilepsy.

Since first described by Charcot[1] in 1876 there have been approximately 177[2] cases reported in the world literature. There has also been much controversy as to the accurate designation of this syndrome. It has been accepted that these cases represent syncope due to cerebral congestion and anoxia secondary to changes in cerebral hemodynamics. Of the cases in the literature only a small number have had electroencephalograms. Of these one was abnormal. However, there is no mention made as to whether any activation was attempted in any of the cases. As will be seen in the following case reports and studies the electroencephalogram contributes much in definitively establishing the proper classification of this interesting syndrome.

CASE HISTORIES

Case 1.—A colored man aged 50 gave no family history of convulsive disorder. He had a history of head injury at the age of 12, and of syphilis in 1937 treated with heavy metals. He had worked as a spray painter for 11 years. Two years prior to examination he had had severe cough which was accompanied by vertigo, and two weeks later he had several generalized convulsions. Two of these attacks were followed by, rather than preceded by, the cough.

Two electroencephalograms showed a random slow wave focus coming from the right frontal area (figure 1). During activation with cough he had a left Jacksonian motor seizure.

Case 2.—A white man aged 59 had a negative family history for convulsive disorder.

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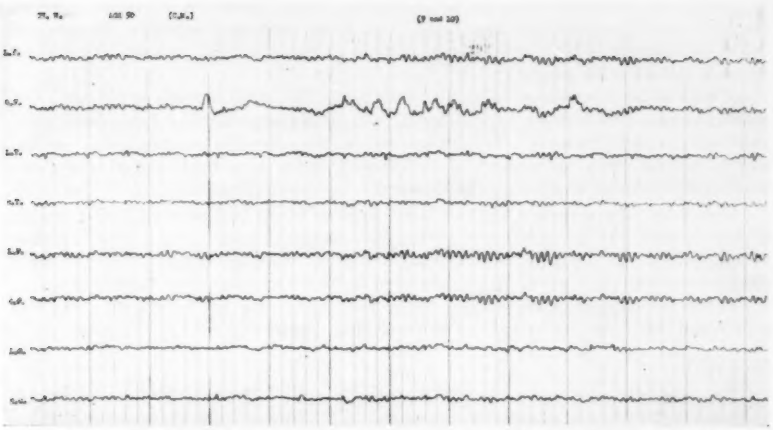

FIG. 1. Random slow wave spikes coming from the right frontal area (case 1).

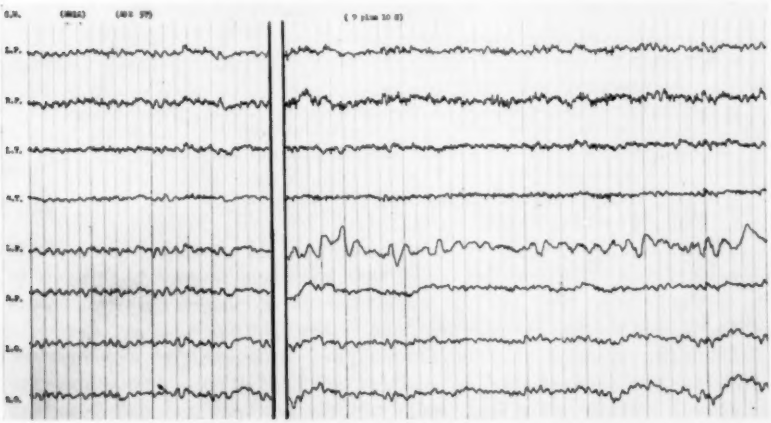

FIG. 2. First section shows a normal record; cough indicated by break in record, immediately followed by slow waves from the left parietal lead (case 3).

He had had bronchial asthma for 20 years. One year prior to examination he had had onset of syncope and right sided Jacksonian motor seizures.

Two electroencephalograms showed a left temporal focus. During one paroxysm of coughing he showed generalized slow waves and spike formations accompanied by clonic movements lasting several seconds.

Case 3.—A white man aged 57 gave a negative family history for convulsive disorder. Eight years previously he had had severe asthma and bronchitis. Seven years later he began to have vertigo with his cough, but had no convulsions.

An electroencephalogram showed a left parietal focus following paroxysm of cough (figure 2).

Case 4.—A white man aged 52 had a negative family history for convulsive disorder. He had severe bronchitis for nine years. Two years prior to examination he had had grand mal seizures which were usually nocturnal. Syncope, and at times convulsions, occurred following the cough.

A total of five electroencephalograms were done. Two were normal, one showed generalized abnormality and the fourth showed a right anterior temporal focus following a paroxysm of cough (figure 3). The patient was put on anticonvulsant medication and has had no seizures either independent of or following cough since beginning treatment and the fifth electroencephalogram was again normal.

Case 5.—A colored woman aged 43 had a negative family and personal history of convulsive disorder. She had evidence of chronic bronchitis with severe cough. One year prior to examination she began to have attacks of syncope with her cough. These occurred several times weekly; however, there were never any focal or generalized convulsions.

Two electroencephalograms awake, asleep and during coughing were taken. One was normal and the second showed a left temporal focus (figure 4).

DISCUSSION

The causes of syncope are many and depend on the sensitivity of the respiratory and vasomotor reflexes. These vary greatly in normals and even more so in those who are sick.

The more common causes of syncope may be listed as follows:

1. Hypoglycemia, either spontaneous or induced.
2. Cardiac diseases.
   (a) Paroxysmal tachycardia.
   (b) Valvular diseases.
   (c) Heart block or the well known Stokes-Adams syndrome.
3. Abnormalities of vascular reflexes (statistically the most important).
   (a) Vago-vagal.
   (b) Glossopharyngeal-vagal or carotid sinus syndrome.
   (c) Postural hypotension.

Tussive syncope is probably an abnormality of the vascular reflexes of the vago-vagal type. The stimulus comes from the vagal sensory end organs in the larynx bronchi, but may also come from the esophagus. Weiss[3] has described a case of syncope resulting from swallowing.

Clinically, syncope must be differentiated from epilepsy and hysteria. While the first differentiation is usually not difficult, there are occasional patients with epilepsy whose early spells are only syncopal, and also those who have unwitnessed seizures of short duration with none of the classical signs such as aura, tongue biting or incontinence. Hysteria offers less of a problem, the differential being difficult only in those patients who have blackouts and vertigo without gross movements. The eletroencephalogram is valuable in the differentiation of these entities.

With regard to the mechanisms involved in producing both syncope and convulsions, certain factors such as (1) abnormal vascular reflexes and (2) abnormal hemodynamics of cerebral circulation have been considered. Wilkins and Friedland[4] have shown that forced expiration alters the hemodynamics of the pulmonary circulation by increasing intrathoracic pressure. This in turn impairs cardiac output and results in cerebral anoxia. As mentioned pre-

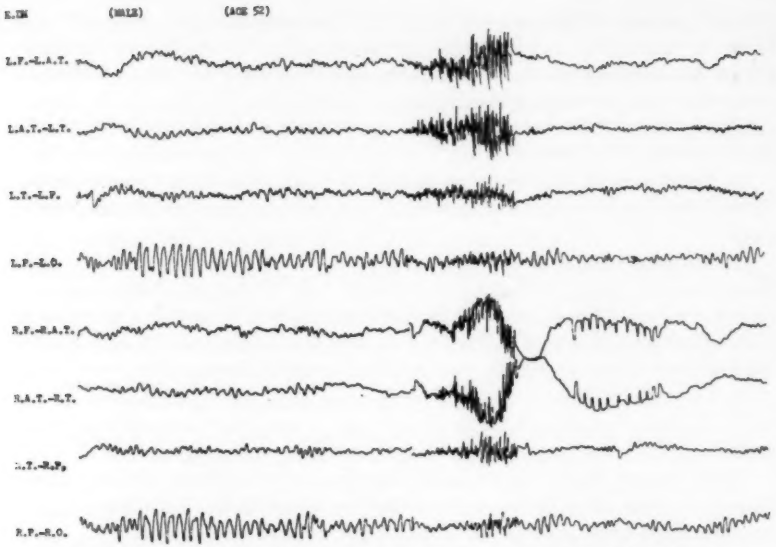

FIG. 3. Record shows normal activity up to paroxyism of coughing (indicated by artifact); following this there are out-of-phase spikes from the right anterior temporal lead (case 4).

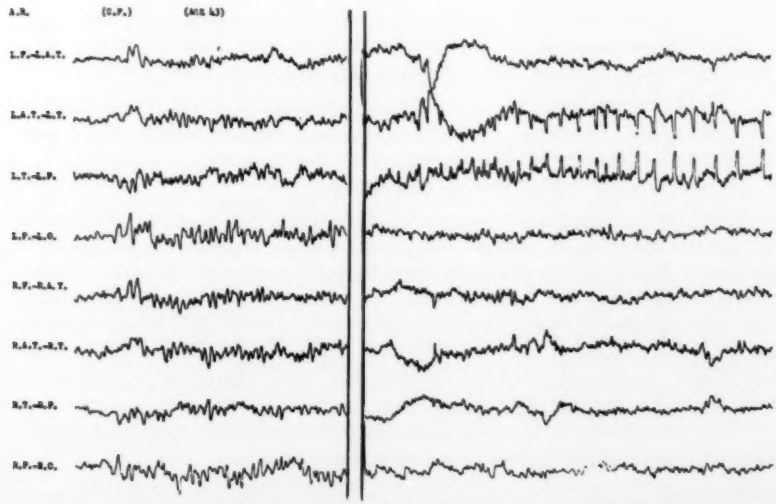

FIG. 4. Normal record before coughing (indicated by break in record); immediately following there are sharp out of phase spikes coming from the left temporal lead (case 5).

viously, patients with tussive syncope show pulmonary emphysema with inability to expire fully, resulting in a chronic buildup of intrathoracic pressure. When the additional stress of coughing is added the same type of cerebral congestion and anoxia result.

That hemodynamic changes alone cannot produce syncope is shown by the following observations:

1. Bridges et al, in a study involving 279 cases of breathholding children, showed that only 0.1 per cent developed cyanosis, unconsciousness or convulsions.[5]

2. Personal studies were made on a group of male medical students free from family or personal history of epilepsy and having no central nervous system disease. The students performed the Valsalva maneuver while having their electroencephalograms recorded; in none was there any change despite the fact that forced expiration was held for at least 35 seconds.[6]

3. Measures inducing cerebral congestion, such as negative acceleration on a centrifuge causing blood to concentrate in the head[6] and obstruction of venous return from the head,[7] fail to produce unconsciousness.

Consequently then, it would seem that there is, in addition to faulty hemodynamics, some other factor, such as that of susceptibility. Furthermore, this factor is most likely an inherent abnormality of cortical function.

This is demonstrated by:

1. Incidence of this syndrome in the older age groups.
2. Incidence predominantly in males.
3. Rarity of the syndrome despite prevalence of bronchitis and cough in the general population.
4. The high percentage of abnormal electroencephalograms.
5. Occasional presence of seizures independent of cough (two cases).
6. Relief of seizures, even following cough, with administration of anticonvulsant treatment (one case).

Further support is derived from the following:

Electroencephalographic studies by Williams show a higher percentage of abnormal records in patients with syncope of all types when compared to controls.[8] Baxter performed electroencephalograms on a group of servicemen who showed syncopal reaction induced by anoxia due to high altitude simulation tests. In nine of ten cases reported there were abnormal records between tests.[9] Whitty reported one case in which syncope occurred at times unassociated with cough and preceded by epigastric aura. This same aura could be reproduced by prolonged coughing.[10]

The average age of all cases in the literature was 47.6 years, and greater than 99.5 per cent of reported cases were men.[2]

CONCLUSIONS

Tussive syncope with or without convulsions cannot be fully explained by the present theories of hemodynamics and abnormal vascular reflexes.

There is a high incidence of abnormal electroencephalograms, indicating a basic susceptibility.

Evidence is provided and supportive evidence is cited to indicate that this basic susceptibility is an inherent cortical dysfunction.

Tussive syncope then would be more accurately classified as a symptomatic epileptic phenomenon.

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At the same time we must remember that the varieties of form give us no clue to the differences that may exist among the elements of which nervous tissues consist. Neither microscopical examination nor chemical analysis can penetrate beyond the coarsest outlines of the constitution of living matter. It is probably within the facts to assert that each nerve-cell contains as many material atoms as the brain contains nerve-cells. Even the molecules, formed by the grouping of these atoms, are beyond the reach of any means of scrutiny we possess, or of which we have, at present, any promise. The fundamental diversity that must exist, where we can discern only uniformity, is shown to us by the action of poisons, and in the effects of disease. One poison acts on one part of the nervous system, and leaves uninfluenced another part, which a second poison affects alone. We are accustomed to explain this by the difference in the chemical constitution of the poison; but it is evidence of an equal difference in the nerve-elements, that are, as we say, "selected" by it. The selection is no matter of arbitrary choice. It is the result of the nature of the nerve-elements themselves; the expression of differences between them, revealed by such effects alone. This consideration renders many effects of disease more intelligible, though it may not lessen their mystery.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Ultracentrifuge Studies of Lipoproteins in Multiple Sclerosis

Robert B. Aird, M.D., John W. Gofman, Ph.D., M.D., Hardin B. Jones, Ph.D., M. Brent Campbell, M.D. and Bill Garoutte, M.D.

IT HAS been evident for a considerable time that the problem of multiple sclerosis will not be solved by clinical, anatomic or histopathologic techniques alone. A considerable body of evidence accumulated over the past decade suggests that a biochemical approach is essential if the etiology of this obscure disease is to be clarified.

Some abnormality of tissue lipid metabolism has been one of the biochemical mechanisms invoked in explanation of the demyelinating process typical of multiple sclerosis.

A review of the literature reveals a number of papers of suggestive import in this conection. Gildea[1] described blood lipid changes in a case of acute demyelination of the central nervous system due to inanition. Weil and Bradburne[2] observed a remarkable alteration of phosphorus metabolism in multiple sclerotics. Their patients were found to be in positive phosphorus balance on an intake as low as 700 mg. per day. Normals, on the other hand, require up to 2000 mg. per day. They suggested that this discrepancy might reflect an abnormality in the phospholipid metabolism of the central nervous system. Brante,[3] and Johnson, McNabb and Rossiter[4] have emphasized that, because of the well-known, high concentration of cholesterol and of conjugated lipids in the myelin sheath, it is probable the demyelinating process is associated with an abnormality of lipid metabolism.

Recent studies by Swank[5] on the correlation between dietary lipids, blood lipids, and the incidence of multiple sclerosis, as found during the lean war years in several European countries, also suggest that fat metabolism may be of considerable importance in this disease. Swank, Franklin and Quastel[6] have

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also studied changes of protein concentration by means of paper chromatography, and have reported typical, though not specific patterns, in patients suffering from multiple sclerosis.

In considering these findings, it seemed possible, if not likely, that lipoproteins, as conjugates of protein and lipid compounds, might show pertinent alterations at some stage of the demyelinating process, especially in view of the findings of Wilmot and Swank[7] and of Fisk, et al.[8] that blood lipids which are not conjugated with proteins do not show alterations.

The changes in cerebrospinal fluid protein in multiple sclerosis are well known. Kabat, Freedman, Murray and Knaub[9] have reported studies which indicate that a portion of the abnormal protein of cerebrospinal fluid may be derived from destruction of the central nervous tissue itself. Changes in the fat content of cerebrospinal fluid in multiple sclerosis apparently have never been observed. However, Janbon, Bertrand and Izarn[10] reported an elevated lipid level in a case of neuromyelitis optica. Such considerations have led us to examine the lipoprotein content of cerebrospinal fluid as well as the blood serum. The purpose of the present report is to present our results, which, however, must still be regarded as preliminary.

MATERIAL AND METHODS

All patients included in the study have been diagnosed and followed by members of the staff of the department of neurology of the University of California School of Medicine. About half of the patients have had additional special studies and have been followed under the Multiple Sclerosis Project of the University of California School of Medicine. Diagnostic studies were performed as required in each case to establish the diagnosis of multiple sclerosis. In addition, the clinical course of each patient was evaluated at the time the specimens were taken to determine whether the disease was, 1) progressing rapidly, 2) progressing slowly, 3) improving, or 4) showing no change.

Serum lipoproteins have been studied by several techniques in the past. The most consistent method has been that employing the ultracentrifugation procedure reported by Gofman, Jones, et al.[11] This technique has been utilized throughout our study in examination of the serum and cerebrospinal fluid of both normals and patients with multiple sclerosis.

Serum was first prepared by allowing drawn venous blood to clot and centrifuging it to remove the clot. The serum was next adjusted to the desired specific gravity (1.063 Gm. per ml. at 26 degrees C.) by adding concentrated saline solution, and then subjected to a preparatory ultracentrifugation at 30,000 r.p.m. for 13 hours. This preparatory step enabled the separation of all unconjugated proteins from the prepared serum.

The deproteinized specimen was finally subjected to ultracentrifugation at 52,640 r.p.m. in a Spinco Model 'E' instrument for 38 minutes, during which time photographic records of the flotation of lipoprotein were made, as described by Gofman et al.

TABLE 1

Patient Number	*Sex*	*Age*	*Clinical Activity*	*Concentration of Sf (12-20) lipoproteins*	*Relative concentration*
1	Male	20	1	44 mg. per cent	93 per cent
1 (repeat)	Male	20½	1	24 "	50 "
2	Female	23	1	41 "	85 "
3	Female	25	1	66 "	99 "
4	Female	27	1	57 "	98 "
5	Male	33	1	49 "	70 "
6	Female	28	2	24 "	50 "
7	Female	30	2	52 "	95 "
8	Female	34	2	35 "	65 "
9	Female	34	2	19 "	15 "
10	Female	35	2	19 "	15 "
11	Female	39	2	23 "	30 "
12	Female	41	2	35 "	45 "
13	Female	42	2	41 "	65 "
14	Female	50	2	62 "	90 "
15	Male	50	2	47 "	60 "
16	Male	51	2	54 "	65 "
17	Male	51	2	19 "	5 "
18	Male	52	2	29 "	25 "
19	Male	57	2	47 "	55 "
20	Female	39	3	21 "	20 "
21	Male	40	4	45 "	55 "
22	Female	41	4	37 "	50 "
23	Female	42	4	49 "	75 "
24	Female	44	4	47 "	75 "
25	Male	44	4	85 "	93 "
26	Male	51	4	24 "	10 "

The cerebrospinal fluid specimens were treated in similar fashion, except, of course, that there was no need to remove formed elements from the fluid.

RESULTS

Lipoprotein studies have been conducted on a total of 28 specimens of serum from 27 patients with multiple sclerosis, and also on 15 specimens of cerebrospinal fluid from 14 multiple sclerotics. In addition, three cerebrospinal fluids from neurologically normal persons were examined. None of the cerebrospinal fluid specimens showed significant levels of lipoprotein. Table 1 presents the serum lipoprotein levels obtained, together with the patient's age, and the activity of the disease as clinically observed in each case.

Lipoproteins, for the purpose of ultracentrifugation studies, are classified according to their rates of migration as they float to the top of a solution of greater specific gravity. The customary unit of migration is the Svedberg (Sf), named in honor of the inventor of the ultracentrifuge. Thus, molecules of the types Sf (12-20) sediment under the influence of a unit field of force at a rate between 12×10^{-13} and 20×10^{-13} cm. per second, while the Sf (20-100) molecules sediment at a rate between 20×10^{-13} and 100×10^{-13} cm. per second. An attempt was made, by means of scatter diagrams, to correlate the concen-

tration of the Sf (12-20) lipoproteins with all known clinical factors of possible significance in the group of patients included in the study.

No correlation was found between the absolute concentration of Sf (12-20) lipoproteins and age, or between concentration and abnormality of the cerebrospinal fluid. Again, no correlation could be established between abnormalities of the cerebrospinal fluid and the relative concentration of Sf (12-20) lipoproteins, as judged by the percentage of normals of the same age and sex showing concentrations lower than those found in the patients studied. On the other hand, there was minimal evidence of an increase in lipoprotein with increased clinical activity of the disease. The cases graded "rapidly progressive" showed levels on the average higher than 82 per cent of normals. The less active cases averaged 50 per cent (i. e., their average fell within the normal range). However, the spread of values is such as to result in a considerable overlap, so that the difference between active and relatively inactive cases is not statistically significant. The results, nevertheless, are suggestive and merit further study.

DISCUSSION

The difference between active and inactive cases, while not statistically significant, still suggests that there may be a slight increase in serum lipoprotein of the Sf (12-20) types in acute stages of the disease. If this increase should be confirmed by further studies, it could be explained by two possible mechanisms. Lipoproteins may be formed as a direct result of myelin breakdown and therefore occur in high concentrations in patients with multiple sclerosis. The comparable concentrations of cholesterol (about 10 per cent)[3,12] found in myelin and in the serum lipoproteins studied might be considered as favoring this possibility.

On the other hand, the elevated concentration of lipoprotein may reflect a more basic abnormality of lipid metabolism. Considering the fact that the absolute amount of demyelination occurring in the plaques of multiple sclerosis is relatively slight and could scarcely account for significant elevations of serum lipoproteins being maintained over prolonged periods in the presence of an active lipid metabolism, the second hypothesis would appear to be more likely. If this second hypothesis is correct and if the suggestive changes reported can be confirmed, they would be related either directly or indirectly to the pathogenesis of the demyelinating process involved in multiple sclerosis, rather than being a result or consequence of the disease.

In view of the obvious limitation of the data, however, further speculation would appear unwarranted. The present findings must be considered preliminary and at best only suggestive of a lipoprotein change in multiple sclerosis. More data, particularly in acutely progressing cases of multiple sclerosis, must be obtained before any definite conclusions can be drawn.

SUMMARY

1. A preliminary report of ultracentrifuge studies concerned with the lipoproteins in the cerebrospinal fluid of 14 patients and in the serum of 27 pa-

tients with multiple sclerosis is presented.

2. The concentrations of the Sf (12-20) and Sf (20-100) lipoproteins in the cerebrospinal fluid were too low to be measured by means of the ultracentrifuge technique.

3. There may be a slight correlation between the degree of activity of the disease process and the level of lipoproteins of the Sf (12-20) types in the serum of patients with multiple sclerosis. The available data, however, are not adequate to establish this relationship as statistically significant. Further studies, especially in patients with acutely progressing multiple sclerosis, are necessary.

We wish to acknowledge our debt of gratitude to all the members of the department of neurology, and of the staff of the Donner Laboratory of Medical Physics who have been of invaluable assistance in referring cases, collecting specimens, and carrying out technical procedures.

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We do not know whether any nerve-fibres unite directly the undivided processes of two-nerve-cells. It is highly probable that, as a rule, they do not, because we usually find that only one process of a cell becomes directly an axis-cylinder; the other processes divide and ramify in a branching network of the finest nerve-fibrilae. This structure is probably intermediate between adjacent nerve-cells, and in it the nerve-fibres may end, that are the prolonged processes of other and sometimes distant nerve-cells.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Perception of Simultaneous Tactile Stimuli in Normal Children

Max Fink, M.D. and Morris B. Bender, M.D.

Normal adults readily identify and localize tactile stimuli applied simultaneously to the face and the hand (the "face-hand test").[1] While half the subjects perceive stimuli incorrectly on the initial trial, all are accurate by the tenth trial of the test. Young children, however, find the task of identification and localization of two skin stimulations difficult. They report only one of the two stimuli, or, if they report the two, frequently mislocalize one of them. The omission or mislocalization of stimuli is not haphazard but follows a consistent pattern in which stimuli to the face are readily appreciated ("most dominant") while those to the hand are not ("least dominant").

In order to determine the pattern of "dominance" in children and the age at which such tactile perceptual tasks are correctly performed, a study of normal children was undertaken. The responses of children to the face-hand test and to simultaneous tactile tests of other body parts were ascertained.

SUBJECTS AND METHOD

Three hundred normal children between the ages of three and 15 were examined. They were from a neighborhood child care center, from the wards and clinics of Bellevue Hospital, and children of neighbors and friends. They were without manifest disorder of the nervous system. A few children at two and a half years of age were included in the three year age group, but younger children were generally not able to comprehend the test.

The subjects were examined individually, but there were many who were examined in a day-room in full view of other children. The child was engaged in play and when toys were available they were used to gain his confidence and interest. At some time during play, the face-hand test was introduced.

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For the face-hand test, the child was told: "I (examiner) am going to touch you," and he was to "touch the same place I touch." He was asked to close his eyes. The examiner, with the fingers, then touched simultaneously a cheek and the dorsum of the contralateral hand of the subject. The child was asked what he felt, and to point to the sites stimulated. After this response, the child was asked to close his eyes again, and now the opposite cheek and hand were similarly stimulated and the report recorded. If only one response was given to this trial, the child was asked if there had been another stimulus anywhere else.

Following these two trials, the cheek and hand on the same side of the body were tested in a similar fashion. The fifth and sixth trials were not of asymmetric body parts but simultaneous stimulation of both cheeks or both hands. The following various types of stimulation were used: heterologous stimulation of asymmetric body parts on opposite sides, as right cheek and left hand; homolateral stimulation of asymmetric body parts on the same side of the body, as right cheek and right hand; and homologous stimulation of symmetric body parts, as both cheeks or both hands. Such tests were repeated in each child until at least ten trials were recorded. Subsequent tests of other body parts, performed in a similar fashion, were introduced until at least 20 consecutive trials were observed in each subject.

A number of modifications had to be introduced for young children. Many would not play the game with eyes closed, but insisted on keeping their eyes open. In such cases the tests were applied with eyes open. Also, a large number of three and four year old children insisted on pointing to the examiner's hands and face on the initial trials. For these children, a few trials of single touch stimuli applied to the thigh, chest or hand were introduced, until they grasped the concept of pointing to their own bodies after the stimulation. These single trials were carried out with eyes open.

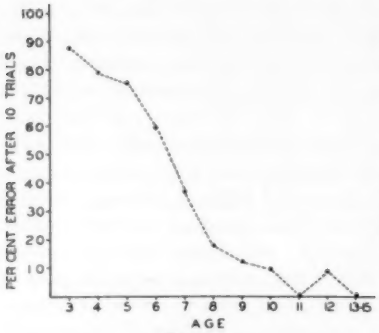
After the series of double simultaneous stimulation tests were completed, single stimuli were applied to various body parts to exclude from the normal group any subjects with focal sensory difficulties.

The children were asked what they had felt and to point to the places stimulated. Verbal reports of the locus of stimulation were not accepted. It was occasionally noted that children would correctly name the parts stimulated, i. e., the cheek and hand, but then point to both cheeks, or to two places on one cheek. It seemed as if naming the locus yielded more accurate responses than did pointing.

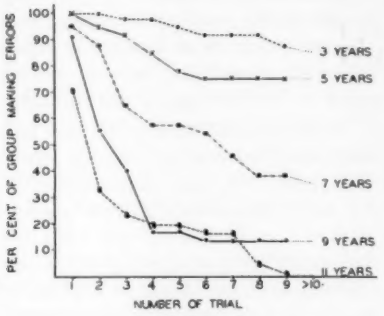
These tactile tests were repeated on consecutive days, or subsequently after a lapse of a few days or weeks in some children. At such times, cutaneous stimuli other than light touch were added to the testing. These included repetitive touch (rubbing), single pin prick, and repetitive pin pricks.

RESULTS

Incidence of errors: Young children made many errors on face-hand tests. Eighty per cent of children under the age of six failed to localize both stimuli



Graph 1.



Graph 2.

during the initial ten trials of the face-hand test; many of these even with eyes open. In the older children the number of failures fell sharply (graph 1) so that only 2 per cent of children in the 11 to 15 year age groups continued to make errors after the initial ten trials. Apparently the ability to identify two simultaneously applied tactile stimuli was directly related to the age of the child. This ability was also related to the number of previous trials of the face-hand test. In table 1 the trial of the test after which the child was consistently correct is recorded. The last column of the table includes all the subjects who made errors in the first ten trials, and on many trials of the test beyond the tenth. Graph 2 illustrates this relation for selected age groups.

Type of testing: In these studies homolateral and heterologous stimulations were carried out at random. Errors were made by subjects of all age groups in tests of either type. Homologous tests, such as both cheeks, or both hands, randomly interspersed in the testing after the fourth trial, elicited correct responses in nearly all cases. While this served as a clue to some of the older

TABLE 1

NUMBER OF TRIALS OF THE FACE-HAND TEST NECESSARY FOR PERSISTENT CORRECT RESPONSES

(Touch Stimuli)

Age	*Total Number of Subjects*	*Trial Correct*									*Errors Beyond 10 Trials*
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
3	39	–	–	1	–	1	1	–	–	2	34
4	34	–	–	1	–	2	2	–	1	–	28
5	37	–	2	1	3	2	1	–	–	–	28
6	36	–	–	1	2	5	4	–	2	–	22
7	26	1	2	6	2	–	1	2	2	–	10
8	22	4	6	3	–	2	1	–	2	–	4
9	23	2	8	4	5	–	1	–	–	–	3
10	20	2	6	5	4	–	1	–	–	–	2
11	21	6	8	2	1	–	1	–	2	1	0
12	24	3	7	4	6	1	–	1	–	–	2
13–15	29	4	10	6	4	2	1	–	–	2	0

children that two stimuli were being applied, it did not seem to alter the results in the younger children. In these subjects subsequent trials of the face-hand test were incorrectly reported, even though the responses to the symmetric stimuli had been correct. The perception of symmetric stimuli was much better than asymmetric stimuli.

Subsequent testing: Of the total group of children studied, face-hand tests were repeated at varying intervals subsequent to the initial testing in 40 children. Of the children under the age of six, subsequent testing elicited the same difficulties with face-hand tests as was evident on the initial examination. In a few children over six years of age, who seemed to have grasped the concept of two stimulations in the initial testing, errors were manifest on subsequent days. It was as if many trials were necessary for successful learning of the task, and then, even though the task was successfully completed, the learning was temporary. These observations are in contrast to those made in normal adults, in whom subsequent testing did not elicit the errors of the initial test.[1]

Type and pattern of responses: The errors (table 1) made by children on repeated trials of the face-hand test were of six types: (a) a touch on the cheek only, implying no perception in the hand; (b) a touch on each cheek, implying a mislocalization of the stimulus applied to the hand; (c) a touch on the cheek, and a second touch on the shoulder, neck or elbow, implying a partial mislocalization of the stimulus applied to the hand; (d) a touch on the hand only, implying no perception in the cheek; (e) a touch on each hand implying a mislocalization of the cheek stimulus to the hand; and (f) one or two touches on the examiner's body, implying a mislocalization away from the child's body.

Face dominance (responses *a, b, c*) was apparent in all age groups. It was most manifest as extinction* of the stimulus to the hand (response *a*), and was seen in 62 per cent of the errors. Mislocalization of the hand stimulus to the cheek (displacement) was observed in 31 per cent of the errors. While most of the displacements were observed in tests involving cheek and hand on opposite sides of the body, 7 per cent of the errors were displacements from the hand to the cheek in the simultaneous stimulation of homolateral body parts, e. g., right cheek and right hand. At such times the child pointed to the cheek once, saying "a touch here," and then, moving his fingers 2 to 3 centimeters lower on the cheek, saying "and here."

Other types of displacement were infrequent. There were partial displacements from the hand to the shoulder or neck. Mislocalization of a stimulus across the midline of the body, known as allesthesia,[3] was occasionally apparent in the stimulus to the hand on heterologous testing. Furthermore, children

*The failure to report one of two simultaneous stimulations has been called "extinction" of a stimulus.[2] The mislocalization of a percept to the homologous body part of the second stimulus is called "displacement." The mislocalization of a percept in the direction of the second stimulus is called "partial displacement." In each instance, the stimulus which is correctly reported is said to be "dominant."

under five years of age frequently mislocalized the initial stimulation away from their body to parts of the examiner's body or into space (response *f*). This phenomenon, known as exosomesthesia,[4] persisted in some children despite repeated stimulations with the child's eyes open, and despite the examiner's insistence that it was the child who had been touched.

Another phenomenon was seen during homolateral testing. The child reported only the stimulus applied to the cheek. If the examiner asked insistently, "Did you feel another touch anywhere else?", a number of children hesitatingly pointed to the symmetrical point in the cheek on the opposite side of the body. In order to determine whether this was a unique or a systematic phenomenon, tests of other body parts were carried out. In homolateral tests of foot and hand, shoulder and hand, and cheek and foot, the same phenomenon was observed. The child first reported only the foot, the shoulder or the cheek—and then, when the examiner insisted on a second locus, pointed to the opposite foot, shoulder or side of the face.

Furthermore, in some young children the phenomenon appeared on single stimulation. Single stimuli applied to any body part were localized correctly. If the examiner then insisted that there had been a second stimulus, the child pointed hesitatingly to the symmetric part on the opposite side of the body.

As already indicated, hand dominance (responses *d* and *e*) was infrequent. It was observed in 7 per cent of the errors on face-hand tests. In all subjects in whom it was apparent, subsequent trials of the face-hand test manifested the pattern of face dominance.

Relation of hand and foot: In tests of parts of the body other than the face and hand, the hand was always least dominant and the cheek the most. Simultaneous tests of foot and hand, the foot-hand test, were introduced after the initial ten trials of the face-hand test in most children. In the foot-hand test, foot dominance was apparent in 51 per cent of the responses (see table 2). It was demonstrated by hand extinction, by displacement of hand stimuli to the foot, and by partial displacement to the thigh, knee and leg.

TABLE 2
FOOT-HAND TEST
(Touch Stimuli)

Stimulation	*Total Trials*	*Responses*					
		Correct	*Foot*	*Hand*	*Foot-Foot*	*Partial Ft.-Ft.*	*Hand-Hand*
Bilateral	53	21	17	1	10	2	2
Ipsilateral	48	23	16	3	3	3	0

Other stimuli: A small group of children who made errors in tests repeated at varying intervals were examined with other cutaneous stimuli. Extinction and displacement phenomena were present in face-hand tests using pin prick, repetitive pin prick and repetitive touch (rubbing) stimulations. While the number of errors with these stimuli were fewer than with touch stimuli, the

pattern of face dominance and hand extinction was still apparent.

DISCUSSION

The ability to identify and localize simultaneous stimuli separated from each other at some distance is a complex function which gradually develops during the first decade of life. It is a relatively unstable ability, for many changes in the state of the organism can disturb such discriminations. Focal cerebral disease as in hemiplegia[5] or parietal lobe lesions,[2] spinal cord lesions,[2] and diffuse brain diseases such as toxic states, senility and inflammatory conditions[6] can so alter tactile discrimination that the phenomena of extinction and displacement become prominent. Errors in simultaneous tactile tests are apparent in normal adults during the initial few trials of the test—during the period of learning.[1] Persons subjected to large doses of barbiturates,[6] electroshock therapy[6] or anesthesia[7] also manifest such inability.

A prominent feature in all groups is the uniformity of face dominance. When discrimination of simultaneous stimuli is interfered with, for whatever reason, the errors are made in the stimuli to the hand and not in the stimuli to the face. The corollary of "face dominance" is "hand extinction." It, too, is apparent in all subjects and under the variety of conditions studied. Furthermore, in an "order of dominance" other body parts are between these two limits. Studies in patients with hemiplegia[5] and patients with severe mental changes as a result of brain disease[6] have revealed an order of dominance of face-shoulder-trunk-thigh-foot and hand. Insofar as these other body parts were studied in these children, a similar order was observed. Since dominance is evident in young children, it appears that the pattern of dominance is an inherent function of the organism. This childlike way of responding to simultaneous tactile stimuli is exposed and exaggerated in adults under a variety of pathologic conditions.

Recently Cohn has suggested a theory of rostral dominance to explain these observations.[8] Our observations are not in accord with such a theory. The dominance of the foot to the hand in children, as well as the dominance of penis, buttock, foot and thigh to the hand in two large series of patients with diffuse brain dysfunction,[6,9] make such an explanation untenable.

Comparison of findings in normal children with findings in patients with organic mental syndrome: On comparing the findings in children with those previously reported in patients with severe mental changes due to brain dysfunction,[6] a close similarity in performance is observed. In both groups the ability to discriminate simultaneous stimuli is limited. On non-homologous tactile tests, such as the face-hand test, errors are made on initial and subsequent trials. While extinction of a stimulus is the most frequent error, displacement is common. In both children and patients, errors occur with a variety of cutaneous stimuli. Furthermore, testing may frequently be done with eyes open, and in many instances with repeated verbal clues that there are two stimuli, and still errors are made. The factor of learning is not prominent since testing on subsequent days will elicit the previous patterned errors.

In Gestalt terms, patients with organic mental defects and children have difficulty in extracting a complex sensory "figure" from the "background" of the total sensory "field." Significantly in each group there is no difficulty in identifying simultaneous stimuli if the stimuli are applied in symmetric regions of the body, such as each hand or both sides of the face. Here, each stimulus figure has a common background in terms of body image, namely the hand.[10]

Face dominance is apparent in both groups. It is manifest not only on tests of face and hand but also on tests of face and other body parts. Also, insofar as it was tested, the order of dominance for other body parts is similar.

While extinction and displacement are the most frequent types of error, other phenomena are elicited in both children and patients. Partial displacements, e. g., the mislocalization of the percept from the hand to the shoulder or neck on the face-hand test, are occasionally observed. The phenomena of allesthesia and exosomesthesia are seen in the more severely affected patients and in the youngest children; both are frequently associated in the same subjects. In allesthesia, the subjects usually localize the cheek stimulus correctly but mislocalize the hand stimulus to the opposite hand or elbow. In exosomesthesia, the stimuli are mislocalized either to space in front of the subject or to the examiner's body. This phenomenon was frequent in the youngest children, and despite the examiner's urging that the child point to its own body, the child persisted in such mislocalizations until a trial of the face-hand test was performed with eyes open.

In addition to these phenomena which appear spontaneously, patients with organic mental syndrome also manifest another response to simultaneous stimulation first noted in children, i. e., on homolateral testing only one stimulus (the cheek) is spontaneously reported; but when the examiner insists, the second is mislocalized to the opposite cheek. Since the patients show so many similarities to young children in their responses, it was predicted that they would also show this phenomenon. In a series of patients with severe mental changes, homolateral tests of the cheek, hand, foot, shoulder and thigh were applied. When only one stimulus was reported, the examiner asked for the locus of the second stimulus. Responses were obtained in 20 per cent of the patients, and in each one the second stimulus was mislocalized to the symmetric body part. Furthermore, in some subjects the same phenomenon was observed with single stimulation.

This phenomenon appears to be similar to the completion phenomenon described in Gestalt literature as "closure" and "good continuation." These are usually described for other sensory modalities. When a circle is tachistoscopically exposed in the visual field so that half falls on a hemianopic field, or if a cross is exposed so that the center falls in the blind spot, many subjects report a complete circle or cross. This "completion" occurs for "good" figures. In simultaneous tactile studies, symmetric figures appear to be the "good" or "strong" figures.

CONCLUSIONS

1. Ability to identify and localize asymmetric simultaneous tactile stimuli develops gradually during the first decade of life, and is present in 80 per cent of normal children by the age of eight. Symmetric stimuli are more readily localized and this ability is well developed in normal three year old children.

2. The errors on asymmetric (bilateral and ipsilateral) stimulation involve either extinction (only one of the two stimuli is reported), or displacement (one or both stimuli are mislocalized). Whenever extinction and displacement occur, stimuli to the face tend to be correctly reported. This face dominance is found at all age levels tested.

3. One can conclude that extinction and displacement of tactile stimuli, as well as face dominance, constitute a normal and consistent pattern of response in children. In addition to these responses one can observe, in children under six years of age, the phenomena of allesthesia, exosomesthesia and partial displacement as normal reactions to simultaneous tactile stimulation.

4. The difficulties in recognition of simultaneous tactile stimuli, as shown by young children, reappear in the same fashion in adult patients with focal or diffuse dysfunction of the brain. The abilities of tactile discrimination acquired by the child during growth are lost by the adult who develops mental changes as a result of cerebral damage.

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Clinical Histologic and Electrical Studies in Muscular Dystrophies

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PART I.—CLINICAL AND HISTOLOGIC STUDIES

Today the pathogenesis and therapy of the progressive muscular dystrophies is just as obscure as it was three-quarters of a century ago when Duchenne,[1] Dejerine and Landouzy,[2] Gowers[3] and Erb[4] wrote their classic papers. No better clinical studies have been made since, and the present diagnostic criteria are the same as they were in 1890. Some knowledge has been gained of basic muscle physiology, chemistry of muscle contraction, disturbances of the creatine metabolism, and nutritional muscular degenerations, and the myotonic atrophies (Steinert,[5] Batten and Gibb,[6] Curschmann[7]) accompanied by various other dystrophic and endocrine disturbances have been described. The many unsuccessful therapeutic attempts present a challenge to greater efforts.

The present situation has led to a renewed study of a number of chronic progressive muscular dystrophies observed in the Veterans Administration Hospital, Hines, Illinois and in the Cook County and Michael Reese hospitals, Chicago, Illinois. Although no satisfactory improvement could be obtained with available therapeutic measures, the classic diagnostic methods enlarged by muscle biopsies, electrical and chemical studies have been used in order to differentiate better the various clinical groups. Some new viewpoints concerning the histopathologic changes are given, and the results of the electrodiagnostic and electromyographic examinations are related to the clinical symptoms.

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TABLE 1-A

SUMMARY OF FINDINGS IN TWELVE CASES OF MUSCULAR DYSTROPHIES

Name	Present Age	Onset	Heredity	Type	Pseudohypertrophy	Endocrinal	Ophthalmologic	Creatine-Creatinine	Hyporeflexia	Spinal	Myotonic signs	Electrical changes	Histologically: Muscle	Nerve
A. Progressive Muscular Dystrophy														
1. Tu.	32	6	0	inf.	0	0	0	+	+	0	0	+	degen-erative	0
2. We.	24	19	0	L.D.	+	0	0	+	+	0	0	0	degen.	0
3. Me.	22	18	0	juv.	0	0	0	±	+	0	0	+	degen.	±
4. Fa.	6	4	0	inf.	+	0	0	+	+	0	0	not done	degen.	±
5. So.	9	5	+	inf.	+	0	0	not done	+	0	0	0	degen.	0
B. Progressive Muscular Dystrophy, Spinal Atrophy														
6. Hu.	53	20	+	L.D.	−	0	0	+	+	±	0	+	degen.	+
7. Fi.	25	8	0	juv.	+	0	0	+	+	±	0	0	degen.	+

0, not found
+, significant
±, doubtful

inf., infantile type
juv., juvenile type
L.D., Landouzy-Dejerine type

Various types of muscular dystrophies exist. They are either primary (idiopathic) or secondary, resulting from denervatory, arthrogenic or vascular disturbances. This paper deals with the primary progressive muscular dystrophies. The 12 cases examined were divided into subgroups according to the clinical, electrical and histologic findings (tables 1a and 1b). Subgroup A comprises five cases of progressive muscular dystrophy. Subgroup C lists four cases of myotonic dystrophy. Tables 1a and 1b show the principal clinical data and their variations in the respective groups. The electrodiagnostic findings, which will be discussed and evaluated in the second part of this paper, were briefly tabulated as "+" or "−" on the tables. Muscle biopsies revealed the actual structural disturbances of the various muscles tested.

What has been called "degenerative" in the column pertaining to the histology of muscle will be detailed in later paragraphs. If finer nerve fibers were present – actually in about 80 per cent of the muscle biopsies – an eventual retrograde degeneration of nerve fibers was tabulated as "+", suggesting an additional spinal cord involvement (subgroup B). That a progressive muscular dystrophy can ultimately affect the anterior motor horn cells has long been known, and two of our advanced and autopsied cases have shown this. However, in myotonic dystrophies degeneration of the anterior grey substance of the spinal cord has not been observed in the 19 cases reported in the literature on whom necropsies were performed (Wohlfahrt[8]). Combinations of muscular dystrophy with myositis were reported long ago by Oppenheim[9] and others. Our case of myotonic dystrophy with myositis, myosclerosis, and pseudohypertrophy deserves special listing (subgroup D).

TABLE 1-B

SUMMARY OF FINDINGS IN TWELVE CASES OF MUSCULAR DYSTROPHIES

Name	Present Age	Onset	Heredity	Begins in:	Pseudohypertrophy	Endocrinal	Ophthalmologic	Creatine-Creatinine	Hyporeflexia	Spinal	Myotonic signs	Electrical changes	Histologically: Muscle	Nerve
C. Myotonic Dystrophy														
8. Hui.	39	32	0	hands	0	testicular atr. baldness	none	+	+	0	+	+	degenerative	0
9. Sh. E	34	28		hands feet	0	testicular atrophy	+	+	+	0	+	+	degenerative	0
10. Sh. R	32	25		r. arm	0	testicular atrophy baldness	+	normal	+	0	+	+	degenerative	0
11. Co.	31	28	0	hands	0	not diagnostic	opacities of lens	normal	+	0	+	+	degenerative	0
D. Myotonic Dystrophy with Myosclerosis														
12. Em.	27	20	0	arms shoulders		not diagnostic	lamelar cataract	normal	+	0	+	+	degen. inflammatory	0

0, not found
+, significant

Here, a painful condition and local swellings at onset of the disease give diagnostically significant hints.

Hereditary or familial trends occurred in all types of muscular dystrophies and were found in one-third of all the cases. The age of onset of the myotonic form was the third and fourth decade of life as compared with the first and second decade in progressive muscular dystrophy. No conclusions could be derived concerning incidence by sex since the male sex prevailed on the neurologic service of the Veterans Administration Hospital.

The progressive muscular dystrophies showed the well-known types of muscular wasting. Three patients belonged to the infantile, two to the juvenile, and two to the scapulohumeral groups of Landouzy-Dejerine; the latter began between the age of 18 to 20 years. Pseudohypertrophy was a common observation (in four of seven cases) in progressive muscular dystrophy and it occurred in all three above-mentioned types. Pseudohypertrophies were missing in the myotonic dystrophies with the exception of case 12, which was apparently the result of a local chronic inflammatory reaction and myosclerosis as proved by muscle biopsies. The myotonic dystrophies presented some or all of the characteristic endocrine and/or ophthalmologic findings, which were absent in the progressive muscular dystrophies. The rate of urinary excretion of creatine and creatinine need not be characteristically altered in a beginning or stationary progressive muscular dystrophy, but in six of our separately tested cases of progressive muscular dystrophy, such findings were positive (+) in

five, doubtful (±) in one patient. Similar examinations of the five long-standing cases of myotonic dystrophy revealed normal findings in three of these. The muscular wasting led to total or partial atrophies and subsequent hypo- and areflexia without sensory disturbances.

The histologic findings revealed in all our cases a degenerative process of varying intensity in different portions of the muscle. Moreover, in biopsies of healthier portions and better preserved muscle substance, some histologic criteria of a primary myodegeneration could be established. Normal nerve fibers and occasionally well-preserved motor end plates in and about degenerating muscle fibers usually indicated an idiopathic muscular degeneration. In the beginning this degeneration was limited to portions of the bizarre-shaped, swollen or shrunken fibers (Kirschbaum[10]). Soon, a disorganized reaction of the muscle nuclei set in and led to an excessive local amitotic multiplication with formation of nuclear clusters. Transverse and longitudinal clefts of the muscle fibers appeared early. During this course of events the perimysial connective tissue was found to be rather inactive. The phagocytic reaction of the reticulo-endothelial system appeared equally retarded, if present at all. Such inactivities of the connective tissue linings at the sarcolemmal membrane can be postulated as an indication of a deficient exchange of, as yet unknown, metabolites at the endomysial-sarcolemmal border.

The histologic findings did not differentiate cases of progressive muscular from myotonic dystrophies, even though the two conditions could be well separated clinically.

The ordinary pseudohypertrophy presented an intensive fat infiltration and fat metamorphosis replacing degenerated muscle substance. It appeared in certain muscles only and was not present in the flat muscle structures such as the diaphragm and intercostal and laryngeal muscles. One case of pseudohypertrophy in myotonic dystrophy was unusual in that it was combined with chronic myositis and myosclerosis.

To differentiate dystrophy from neurogenic muscular atrophy with subsequent muscular degeneration, one observes the integrity of the nerve fibers and the absence of a preceding retrograde degeneration of the axons with proliferation of the Schwann cells.

SUMMARY

1. Seven patients with progressive muscular dystrophy and five patients with myotonic dystrophy were examined clinically and histopathologically.

2. The clinical symptomatology permitted differentiation of these primary muscular dystrophies and the data are presented under four subgroups.

3. Familial or hereditary factors were found in two cases of progressive muscular dystrophy, and in two cases of myotonic dystrophy.

4. Pseudohypertrophy was seen in four cases of progressive muscular dystrophy and in one unusual case of myotonic dystrophy with myositis.

5. Testicular atrophy, baldness, and cataracts, single or combined, were

frequently observed in myotonic dystrophies and were absent in progressive muscular dystrophy.

6. Progressive muscular dystrophy may have progressed to degeneration of the spinal motor neurons in two cases. Spinal cord changes in myotonic dystrophies were not observed.

7. The histologic criteria for a primary myodegeneration include normal nerve fibers and well-preserved motor end plates in and about degenerating muscle fibers. This degeneration is limited to portions of the bizarre-shaped, swollen or shrunken fibers which soon lead to a disorganized reaction of the muscle nuclei and excessive local amitotic multiplication with formation of nuclear clusters. Transverse and longitudinal clefts of the muscle fibers appear. The perimysial connective tissue was found to be rather inactive as was the phagocytic reaction of the reticulo-endothelial system.

8. There were no histologic differences between idiopathic and myotonic dystrophy.

PART II.—ELECTRICAL STUDIES

Electrodiagnostic aids in neurologic diseases have been used since Erb's monumental contribution in 1865. These aids consisted of characteristic responses to faradic (alternating) and galvanic (direct) currents. Electromoygraphy as an aid is of more recent origin and is still in the research and experimental stages, although used clinically by a few of the more electronically-experienced clinicians.

Electromyography is hampered in becoming more popular because of lack of standardization of apparatus and lack of uniformity in observations and descriptions. With the advent of Adrian-Bronk needle electrodes which were first used by Lindsley and Currien[11] in 1936, wave form differences in electromyography could be studied.

Thomasen[12] in his monograph on "Myotonia" summarizes Buchthal and Clemmesen's electromyographic examinations in 21 of their combined patients. Six were ordinary dystrophies and 16 were myotonic. They did not include complete galvanic examinations. In myotonic dystrophies using needle electrodes they observed showers of electrical activity which was almost pathognomonic. In certain cases the frequency was rapid and decreasing; others slower frequency but increasing. The audioamplifier sounded like a growling dog with occasional single potentials oscillating like crackles. These lasted ½ to ½ msec. As in Brown and Harvey's[13] description, irritability increased so that touch, a needle, or percussion caused activity of a frequency of 100 to 150 per second which slowed down to 20 or 10 per second. During voluntary contraction it was difficult to obtain single potentials, as on slight contraction in normal muscle, but interference patterns resulted. No difference was found in congenital or dystrophic myotonia. Brown and Harvey were able to produce myotonic contraction in a denervated, curarized myotonic goat muscle by

intra-arterial injection of potassium chloride. They exclude myotonia as a central nervous system reflex and feel the site of origin is distal to the peripheral motor neuron.

As additional evidence, Buchthal and Lenhard were able to stimulate a curarized lizard muscle with potassium chloride but not with acetylcholine. They concluded that the motor end plate has two separate functions: a nervous and muscular portion. After curare paralyzes the nervous or motor portions, the muscular part can emit normal impulses.

In myotonia the end plate must be abnormally sensitive to stimuli, so that a series of action potentials are emitted instead of normal single action potentials on ordinary volition. Clinically this is borne out in that on irritation of muscles single action potentials are fired rapidly, while on volition these same potentials cannot be demonstrated and an interference pattern results.

Kugelberg, after studying the duration of normal potentials, summarizes the electromyographic diagnosis of dystrophy: (1) increase of polyphasic potentials which are narrower than normal; (2) interference activity even in marked weakness.[14]

Galvanic abnormalities are given vaguely in literature and in textbooks. Brock mentions slight increases in chronaxie in muscular dystrophy and possible increase in rheobase threshold.[15] In myotonia, muscular contraction is prolonged and again mention is made of lengthened chronaxie even greater than in reaction of degeneration. In contrast to reaction of degeneration, myotonia can be produced by faradic current. In myotonia of tetany, the chronaxie may be three times the normal.

Since none of the textbooks give much more data, it was our feeling that complete examination by every modality might be helpful.

PROGRESSIVE MUSCULAR DYSTROPHY

Electrical studies were done on 13 cases, seven of whom were considered pure dystrophies (although one was thought to be mixed atrophy and dystrophy) and six of whom were diagnosed as myotonic dystrophy or myotonia atrophica.

For the most part, this electrical study included a galvanic examination (using the Golseth-Fizzell square wave stimulator) giving data including rheobase, chronaxie, strength duration curve, galvanic tetanus ratio (cathodal and anodal), polar ratio, repetitive stimuli curve, and spread of contraction. The response to faradism was also noted (table 2).

Electromyographic examination was done with needle (unipolar) electrodes. Spontaneous units, active motion potentials, and fibrillation units were noted, and also response to mechanical irritation. The size, shape and frequency of units could be studied by means of continuous photography of the cathode ray oscilloscope screen.

Muscular dystrophy: Of seven patients, 15 muscles in five patients were examined electrically. The *rheobase* ranged from 2.0 to 7.5 m.a. with a median of 4.9 m.a. which could be considered normal.

TABLE 2

ELECTRICAL FINDINGS IN MUSCULAR DYSTROPHY
(7 patients)

Rheobase	Chronaxie	Galvanic Contraction	Faradic Contraction	Polar Ratio
Range 2-7.5ma. Median 4.9ma. Normal 15 muscles 5 patients	Range 1-7msec. Normal 1.0	Slowed 56%	1.0 in mixed dystrophy and atrophy	Decreased in 50% Range (.72-1.3) Normal over 1.5
Cathodal Tetanus Ratio	**Anodal Tetanus Ratio**	**Repetitive Stimuli**	**Strength Duration Curve**	**Electromography**
Decreased 50%	Decreased in muscles of 2 patients	Normal	Normal	Normal Potentials

ELECTRICAL FINDINGS IN MYOTONIC DYSTROPHY
(21 muscles in 6 patients)

Rheobase	Chronaxie	Galvanic Contraction	Faradic Contraction	Polar Ratio
Range 0.8-6.6ma. Median 2.3ma.	Range 1.5-40msec. Median 5.0msec. Normal 1.0	Slowed in 80% of 21 muscles	Decreased in 10% with myotonic response	Decreased in 15% of 19 muscles Range 0.5-1.6
Cathodal Tetanus Ratio	**Anodal Tetanus Ratio**	**Repetitive Stimuli**	**Strength Duration Curve**	**Electromography**
2.0 or less in 80% Normal 3.5+	1.0 in 44% less than 2 in 70%	Ascending in 65%	Steep	a) Spontaneous narrow potentials in 3 b) Myotonic response in 80% on tapping c) Narrow irritation potentials 65% d) Fasciculation 20% (21 muscles in 6 patients)

The *chronaxie* in 14 muscles ranged from 1.0 to 7 msec. In five, or 35 per cent, the chronaxie range was from 1.5 to 7 msec. The rapidity of contraction was decreased in eight of 14 muscles and was plus 1 to plus 2 (normal equals plus 4). *Faradic* response was decreased in seven of 14 muscles. The *polar ratio* was less than normal in 50 per cent, being 0.72 to 1.3 (normal being over 1.5).

The *cathodal tetanus ratio* was abnormal (1.0) in two muscles (normal 3.5) of one patient who had a mixed picture (including atrophy). The *anodal tetanus* ratio was decreased in two muscles of two patients.

The *repetitive stimuli curve* was descending or normal in 12 muscles (one had high thresholds).

Electromyography in 13 muscles revealed no abnormalities such as fibrillation. In only one were narrow potentials observed and one had low voltage potentials. At this time our feeling was that there were no diagnostic electrical abnormalities in this group of muscular dystrophies.

Myotonic dystrophies: Twenty-one muscles of six patients were examined electrically. The *rheobase* range was less than in pure dystrophies (0.8 to

6.6 m.a.) with a median of 2.3 m.a. as compared with a median of 4.9 m.a. in pure dystrophies.

Chronaxie was elevated in 16 of 21 muscles (80 per cent) from 1.5 to 40 msec., with a median of 5.0 msec. The contraction was slowed in 16 or 80 per cent of 21 muscles. The *faradic* response was decreased in 10 of 21 muscles with after contraction noted.

The *polar ratio* was decreased in 15 of 19 muscles (0.5 to 1.6 – normal being over 1.5).

The *cathodal tetanus ratio* in 21 muscles was abnormally low in 17, or 80 per cent, being 2.0 or under (normal greater than 3.5). In 11 muscles it was 1.0 to 1.1. In 14 it was 1.0 to 1.4. *Anodal tetanus ratio* in 16 muscles was 1.0 in 7 muscles. In 11, or 70 per cent, it was under 2.0. In five muscles cathodal tetanus ratio was greater than anodal tetanus ratio (normally, anodal tetanus ratio is greater than cathodal tetanus ratio).

Repetitive stimuli curves were abnormal in 13 of 20 muscles and were of the ascending type.

Electromyography revealed spontaneous narrow units resembling fibrillation in three muscles. Narrow potentials on action or irritation were noted in 13 muscles.

Myotonic response or contraction to irritation such as tapping was present in 16 of 20 muscles. When this occurred the frequency of units firing was so rapid as to give an "aeroplane dive" or "buzzsaw" sound on the audio-amplifier. Fasciculatory units were noted in four muscles.

All of these responses are similar to those found in denervated muscle with the exception that myotonic muscles react to faradism and other repetitive stimuli with a delayed release, while denervated muscle does not usually contract to stimuli of short duration.

SUMMARY

1. Electrical studies were done on 13 patients: seven were diagnosed progressive dystrophy including one mixed case with spinal atrophy; six were myotonic dystrophy.

2. In five of seven patients with muscular dystrophy,
   (a) Rheobase ranged from 2.0 to 7.5 m. a. with a median of 4.9 m. a.
   (b) Chronaxie in 14 muscles ranged from 1.0 to 7 msec.; in 35 per cent the chronaxie was elevated from 1.5 to 7 msec.
   (c) Speed of contraction was decreased in eight of 14 muscles.
   (d) Faradic response was diminished in seven of 14 muscles.
   (e) Polar ratio was decreased in 50 per cent of the muscles.
   (f) Tetanus ratio was normal excepting in the one patient with mixed spinal atrophy.
   (g) The repetitive stimuli curve was normal.
   (h) The strength duration curve was normal.
   (i) Electromyography in 13 muscles showed narrow potentials and low voltage in only one patient.

3. In the six patients with myotonic dystrophy 21 muscles were examined.
   (a) The rheobase range was 0.8 to 6.6 m. a. with a median of 2.3 m.a.
   (b) Chronaxie was elevated in 80 per cent from 1.5 to 40 msec. with a median of 5.0 msec.
   (c) The speed of contraction was decreased in 80 per cent.
   (d) The faradic contraction was decreased in 10 per cent with a myotonic response (delayed release).
   (e) The polar ratio was decreased in 15 per cent of the muscles.
   (f) The tetanus ratio was less than 2.0 in 80 per cent of the muscles.
   (g) The repetitive stimuli curve was abnormal or ascending in 65 per cent.
   (h) The strength duration curve was abnormally steep.
   (i) Electromyography revealed
      (1) Narrow potentials some of which were spontaneous
      (2) Myotonic response to tapping causing musical sounds, of a frequency of 100 to 150 per second
      (3) Fasciculatory potentials
4. Myotonic dystrophy has characteristic electrical changes in contrast to progressive muscular dystrophy.

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Bilateral Anterior Cingulate Gyrus Lesions

Syndrome of the Anterior Cingulate Gyri

Ralph W. Barris, M.D. and Harold R. Schuman, M.D.

A 40 year old man had been ill for three days prior to his hospital admission. When examined, he was mute, akinetic, indifferent to painful stimuli, and incontinent of urine. His eyes were open; deep tendon reflexes were intact; bilateral Babinski signs were present; muscle tone was normal; he was unable to swallow foods and liquids fed to him; his pupils were of normal size and pupillary reactions to light, both direct and consensual, were normal. Thus by clinical standards, he was unresponsive to external stimuli, yet not in coma. At necropsy bilateral lesions were found in the anterior cingulate gyri.

This patient resembled in many ways the case recently reported by Nielsen and Jacobs[1] in which there was found at necropsy a destructive lesion involving the anterior cingulate gyri and the underlying corpus callosum. In a subsequent paper Nielsen[2] analyzed the symptomatology referable to bilateral lesions of the anterior cingulate gyri. He also drew attention to the clinical differences between cases in which lesions involved only the corpus callosum and of those in which both the corpus callosum and projection fibers from both cingulate gyri were involved. The present study emphasizes the similarities of these cases.

CASE REPORT

Present illness: Three days prior to hospital admission, this 40 year old white salesman experienced a transient "jerking" movement of the right lower extremity, and a second similar episode three hours later. During each of these episodes he appeared neither able to reply to questions nor capable of spontaneous speech. His recovery was rapid after each

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episode and apparently complete, and he left his home shortly thereafter for his usual employment activties.

He returned home about eight hours later. It was then that his family noted marked changes in his usual demeanor. He was said to be quite apathetic and indifferent to his surroundings. While he held the newspaper in front of him, he did not seem to be able to keep his attention on it. While sitting on a couch he was incontinent of urine, but seemed indifferent to this incident.

On the morning of the following day, apathy and indifference were even more evident; there was noted an increasing impairment of ability to maintain attention or to concentrate. A rather ill-defined clumsiness and slight unsteadiness in walking were noted. During a television program that afternoon he asked repeatedly what program he was seeing. He was again incontinent of urine and indifferent to the incident. On the morning of the following day he was found sitting on the floor of his room ineffectually and rather implausibly polishing a cigarette lighter. At that time he did not reply verbally to questions nor speak spontaneously. Members of his family thought he comprehended their questions, however. In addition, they noted a lack of spontaneity and of motor initiative. They stated, "he seemed to know what he wanted to do, but couldn't do it."

He was brought to the hospital at about one o'clock of that day, the third day of his illness, his condition having gradually deteriorated during the forenoon.

Past history: The patient sustained a head injury followed by several days of coma in 1935. He had had occasional generalized grand mal seizures since that time.

Examination: The patient was lying supine in bed, making no reply to questions nor responding to verbal commands. Urinary incontinence was evident. His eyes were open; the eyeballs moved slowly in random fashion. His eyelids blinked frequently. When an attempt was made to examine his oral cavity or to open his mouth, he clamped his jaws and held them firmly clenched. Passive hyperflexion of the neck was resisted by a voluntary hyperextension of the neck, but nuchal rigidity was not thought to be present. Examination revealed blood pressure: 130/20; pulse: 100; temperature: 100.4° F.; respirations: 26/min., somewhat shallow and irregular in character. Cutaneous surfaces of the body were warm and dry to the touch; palms and soles were slightly moist. Further examination revealed all deep tendon reflexes to be intact and of about normal vigor. The ankle jerks, however, were absent. Cremasteric and abdominal reflexes were absent. Bilateral Babinski signs were present. Muscle tone was approximately normal. However, a questionable mild generalized muscle hypertonia was noted at times during the course of the examination. There were no spontaneous movements of the limbs or body. No visible reactions to pain could be detected even during firm testicular compression, Achilles tendon pinching, or pressure over the supra-orbital notch. On one occasion, however, during firm testicular compression, the left hand was observed to move slightly. Pupils were of normal size and reacted in a physiologic fashion to light, both directly and consensually.

Laboratory studies: Skull x-rays, initial blood count, urinalysis, and blood serology were all within normal limits. The spinal fluid on admission was clear, the initial pressure 260 mm. of water, and except for 26 red blood cells, was normal with respect to cell count, total protein, globulin, gold curve and Wassermann reaction. Blood urea nitrogen, creatinine, serum chlorides, sodium, and potassium, blood CO_2, blood sugar, blood bromides, and sedimentation rates were all within normal limits.

Course: During the first 24 hours the patient's appearance remained essentially unchanged except for the following: the temperature rose gradually to 103.5° F. (rectally); pulse and respiration rates accelerated to 130/min. and 38/min., respectively; voluntary swallowing of foods and liquids became more sluggish, and a tendency for "pooling" of saliva requiring occasional aspiration was noted. Typical of observations recorded in the nurses' notes during the first 24 hours were such statements as: "Awake, but does not re-

spond when spoken to;" "coughs but seems unable to expectorate"; "is able to swallow sips of water."

Bilateral trephination and ventriculography were done on the second day of hospitalization, and demonstrated no abnormalities. These were suggested by neurosurgical consultants to rule out a possible subdural hematoma or other type of space-occupying lesion.

On the fourth hospital day swallowing activities, both voluntary and reflex, had become so greatly impaired that tracheotomy was carried out to obviate repeated aspiration of saliva from the throat and to improve the respiratory exchange. Intravenous feedings were instituted. The eyes remained open, the eyelids blinked occasionally, and the eyeballs moved slowly at random. The patient remained mute and unresponsive to all forms of painful stimulation; deep tendon reflexes disappeared, though Babinski signs were still in evidence.

By the fifth hospital day swallowing movements were no longer noted; the pupils had become constricted and unresponsive to light; temperature, pulse, and respiration, which had been gradually rising since the day after admission, had now reached 106.4° F. (rectally), 120/min. and 64/min., respectively. Portable type chest x-rays were taken on the second and fourth days, and were said to show a mildly increased density in the left basilar region, compatible with an early bronchopneumonia. Penicillin and Streptomycin administration were begun on the second hospital day and continued throughout his hospital course, but were without noticeable effect on the gradually rising temperature, pulse, or respiration rates.

During the next 15 days the patient's condition remained relatively stationary. The white blood count ranged between 9,000 and 11,000 with a normal differential, except for one white count on the second hospital day of 19,000, the differential count not being reported on that occasion. Temperature during his entire hospitalization ranged between 101° F. and 106.4° F. (rectally), usually above 103° F.; the pulse rate ranged between 102 and 140, usually above 120; and respiration rates ranged between 32 and 60, usually above 36/minute. In the last 10 days of the 20 day hospital period the spinal fluid changed from the normal findings noted on admission to those showing a gradual elevation of total protein (278 mg.), a first zone gold curve (5555544221), a 3 plus globulin, a negative Wasserman, and 75 white cells (90 per cent lymphocytes, 10 per cent polymorphonuclear cells), this report being the last of three spinal fluid studies accomplished during the last ten days. The patient expired on the twentieth hospital day. Pulse and respiration had finally become weak and irregular during the last hours of his illness.

Necropsy: At the time of postmortem study, the brain was perfused with formalin and gross sections of the hemispheres were made in a coronal fashion. These revealed an extensive area of hemorrhagic discoloration and softening in the region of the anterior cingulate gyri, more extensive on the left than the right. There was no evidence on gross inspection of encroachment of the lesions on the underlying corpus callosum (figure 1). After placing the slabs together, the corpus callosum was sectioned longitudinally, and the medial surfaces of the hemispheres exposed. It was seen that the lesions were confined almost exclusively to the anterior cingulate gyri. The lesion was more extensive on the left than the right, however, and appeared to involve not only the anterior cingulate gyrus (area 24) but to encroach slightly on the contiguous cortical areas roughly corresponding to the inferior-medial portion of areas 4 and 6 (Brodmann), with a possible slight encroachment on area 32 (figures 2 and 3). In the orbitofrontal area, bilaterally, and on the under surface of the left temporal lobe, there was noted a "moth eaten" appearance and brownish discoloration, thought to be residuals of an old malacia incurred as a result of head injury many years prior to his present illness.

Microscopic study of coronal sections of right and left sides of the hemispheral areas involved by the lesions revealed that the anterior cingulate gyri were involved bilaterally with areas of liquifaction necrosis ("gitter cells") and hemorrhagic infarction, the destruc-

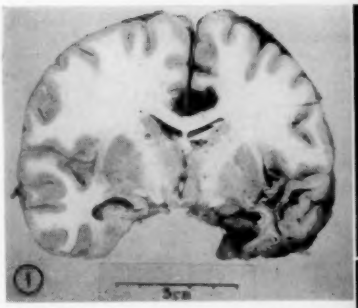

FIG. 1. Gross appearance of bilateral cingulate gyrus lesions, coronal section, rostral surface.

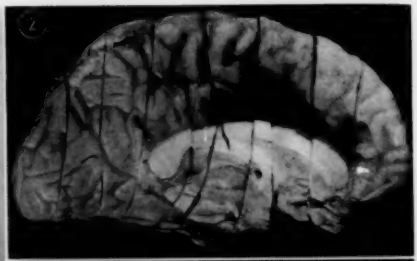

FIG. 2. Medial view, left hemisphere, showing gross appearance of cingulate gyrus and adjacent cortical lesion.

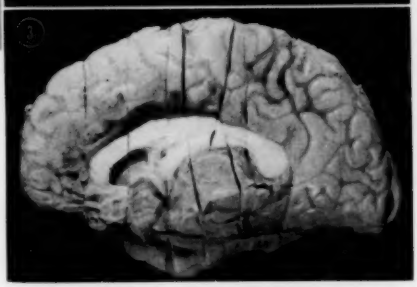

FIG. 3. Medial view, right hemisphere, showing gross appearance of lesion of anterior cingulate gyrus.

tion extending deeply into the underlying white portions of the cingulate gyri, more on the left than the right. At the level of the lesion's greatest extent, along the left medial surface, there was noted microscopically the slightest encroachment of the lesion along the most dorsolateral aspect of the corpus callosum, involving only a few of the fibers of the callosum at this point. Except for this, microscopic study of cell (cresyl violet, Gomori's trichrome, hematoxylin and eosin) and myelin sheath stained (Weil) sections revealed the corpus callosum to be essentially intact (figure 4).

FIG. 4. Low power view, coronal section, showing areas of necrosis involving cingulate gyri bilaterally. (Gomori's trichrome stain.)

DISCUSSION

The clinical features of the case herein reported were quite similar to that recently reported by Nielsen and Jacobs.[1] The earlier signs and symptoms were those of apathy associated with eventual akinesia and mutism; the later

TABLE 1

COMPARISON OF CLINICAL FEATURES OF PRESENT CASE WITH THAT REPORTED BY NIELSEN AND JACOBS[1]

	Nielsen's Case	*Present Case*
Apathy → stupor → coma	+	+
Akinesia	+	+
Mutism	+	+
Urinary incontinence	+	+
Integrity of deep tendon reflexes	+	+
Bilateral Babinski signs	+	+
Ultimate death	+ (34 days)	+ (23 days)
Postmortem Findings:		
(a) Bilateral cingulate gyrus lesions	+	+
(b) Corpus callosum lesion	+	0

stage of the clinical course was characterized by a deepening stupor progressing to a final state of coma, followed after several days by death. In addition, the case reported by Nielsen and Jacobs and the case reported herein were similar in the earlier course of the illness, with respect to the integrity of deep tendon reflexes, the onset of urinary incontinence, and bilateral Babinski signs (table 1). It was Nielsen's[2] view that bilateral cingulate gyrus lesions result in a clinical picture, the earlier stage of which has been referred to by him as characterized by "akinetic mutism" (stage II), and the later (terminal) stage of which is characterized by progressively deepening stupor and coma (stage III). He also felt that in certain previously reported cases of "central necrosis of the corpus callosum" (Marchiafava's disease[3]), the earliest symtoms of anxiety, over-activity and irritability, and various degrees of psychotic behavior seen in this disease were a reflection of the collosal involvement (stage I). It was felt that the later signs and symptoms occurring in some of these patients were a reflection of the progressive lateral extension of the callosal necrosis in consequence of undermining of projection fibers of the anterior cingualte gyri; that in effect, stage II ("akinetic mutism") and stage III ("terminal stage") of the clinical course noted in some cases of Marchiafava's disease were reflections not of callosal necrosis but of the lateral extension of the necrosis, with final undercutting of the anterior cingulate gyri (table 2). The case of bilateral cingulate gyrus lesions reported here, therefore, is of especial interest in that the symptomatology of stages II and III (of Nielsen) were in evidence, without any of the antecedent signs or symptoms of stage I. The previous reports of Nielsen and Jacobs[1] and Nielsen,[2] and the present report call attention, therefore, to a symptomatology which is so characteristic as to probably constitute a syndrome—the syndrome of the anterior cingulate gyri (table 1).

The importance of clinical cases of this type is further emphasized by the attention which has recently been given to the functions of the cingulate gyri.

TABLE 2

CORPUS CALLOSUM-CINGULATE GYRI SYNDROME

Callosal Lesion (Stage I[2])	*Cingulate Gyri Lesions* (Stage II[2])	*Cingulate Gyri Lesions (?)* (Stage III[2])
Emotional excitement: (anxiety; restlessness; irritability; tremulousness; etc.)	*Akinetic mutism*: (apathy; indifference to pain; thirst, hunger; absence of motor and psychic initiative; integrity of deep tendon reflexes; bilateral Babinski signs; open eyes)	*Terminal Status*: (stupor → coma → death)

The question, for example, has been raised as to whether some of the results of prefrontal lobotomy may not in essence be due to section of the projection fibers from the anterior cingulate gyri (area 24)[4]. Likewise, the question has been raised as to whether the symptomatology of patients with tumors of the corpus callosum may not be due to damage to the contiguous cingulate gyri, rather than to the corpus callosum, per se.[5] Schlesinger,[6] for example, has recently reported on an analysis of 20 cases of glioma of the corpus callosum, emphasizing the constancy of mental changes in each of the patients of his series; inasmuch as surgical section of the corpus callosum does not give rise to deterioration in any of the higher intellectual functions, Schlesinger attributed this symptomatology to involvement of adjacent cortical structures by the callosal glioma. Schlesinger also pointed out that "affective disturbances," particularly of "drive and euphoria," were more frequently encountered when callosal tumors involved the cortical areas contiguous to the genu and rostrum of the callosum, in contradistinction to the less specific symptom of "disturbances of memory" noted when more posterior structures contiguous to the splenium were involved by the callosal tumor.

In subhuman mammals, studies on the anatomy of the anterior cingulate gyri have revealed them to be projectional areas of the frontal lobe, and not simple associational areas as formerly thought, nor belonging to the olfactory cortex.[5] Strychninization studies have demonstrated intracortical projections from area 24 to areas 31, 32, 6a and 4s, and subcortical projections to the caudate nucleus.[7,8]

Retrograde cellular degeneration studies have demonstrated projections from the anteromedial nucleus of the thalamus,[9,10] and Marchi degeneration studies[8] have revealed projection fibers leaving area 24 to reach the medial reticular formation of the pons. Thus, the primary afferent connections of the anterior cingulate gyri are from the hypothalamus, via the mamillothalamic tract, through the anterior thalamic nuclei to area 24; and the chief efferent projections are to the caudate nucleus and medial reticular formation of the pons.

In subhuman mammals, bilateral ablation of anterior cingulate gyri (area 24) in monkeys was accomplished by Smith[11] who in 1944 reported that fol-

lowing this procedure his monkeys would sit for long periods without signs of motor activity. They were hypokinetic, appeared much less frightened when approached (apathetic), and took food readily from the human hand (indifferent to fear). Ward[12] in 1948 reported after similar bilateral ablations that his monkeys manifested what he chose to call a "social indifference" to fellow monkeys, and a loss of mimetic activity, grooming, and signs of affection. It was his view that the anterior cingulate gyri play a major role in the elaboration of functions of central emotion as well as a participation in the functions of emotional expression.

In the human, except for the report of Nielsen and Jacobs,[1] and the present case report, no reports of clinical observations referable to patients with spontaneously occurring bilateral anterior cingulate gyrus lesions have been made. However, neurosurgeons have recently made efforts to ablate the antrior cingular gyri (topectomy) in search of a procedure which would more effectively benefit the agitated, aggressive and overactive psychotic, with the goal of leaving the intellectual functions unimpaired. The first report of this type was that of Le Beau and Pecker[13] who in 1950 described eight cases, one of which died postoperatively. These cases increased to a total of 20 by April 1950.[5] All were carried out for the purpose of relieving psychomotor agitation and anxiety. All were said to have improved, several very markedly. Cairns, in December 1950, reported that following bilateral "cingulectomy," 41 patients who had been afflicted with anxiety neuroses and obsessional states were "conspicuously improved."[5] Livingston,[5] in January 1951, reported that he had carried out bilateral "cingulectomies" in a series of 51 psychotic patients and that 28 of these had been followed postoperatively for one year or more. Of the operated cases, 15 were sufficiently improved so that they were admitted to the privileged ward of the hospital. He felt that the benficial changes in behavior of the violent and aggressive cases were strikingly similar to the behavioral changes earlier described in cingulectomized monkeys by Ward[4] in 1948. Livingston believed that the results with cingulectomy were qualitatively much superior to the response obtained with the standard "radical" lobotomy of Lyerly-Poppen. Cairns and Livingston attesting to the value of the cingulate operation in anxiety states, and in aggressive psychotics, were unable to find evidence of intellectual impairment following this procedure.

In the light of these clinical observations on humans who have survived neurosurgically induced "anterior cingulectomies," it might well be asked why, in the case reported by the present authors and in the case reported by Nielsen and Jacobs,[1] the symptomatology was so profound, with symptoms of complete akinesia and mutism, and why in our cases apathy was eventually followed by stupor, coma and death? The only possible answer that seems adequate at this time is that there is probably some difference in the degree and extent of the anterior cingualte gyrus lesions in the two sets of cases, the spontaneous lesions being perhaps more extensive than those of the topectomies. Inasmuch as the cases with surgically induced cingulate lesions are still

living, it may be some time before the extent of the surgically induced lesions can be ascertained. This question must therefore remain unanswered for the time being. However, if one recalls the mid-line location of area 24, it is not difficult to believe, because of relative inaccessibility, that the surgically induced anterior "cingulectomies" were not really "cingulectomies" but probably "cingulotomies," thus not being as completely destructive of the anterior cingulate gyri as in those cases where extensive anteroposterior lesions have occurred spontaneously.

Of special interest in the present case were the persistently elevated temperature, pulse and respiration rates and ultimate onset of coma. Inasmuch as massive doses of antibiotics failed to influence these signs and because the white blood cell counts remained within normal limits, it does not seem probable that these abnormalities were a reflection of some coincidental inflammatory or hidden infectious process. It seems more probable that these findings were a reflection of a neurogenic type of imbalance, especially of the autonomic regulatory mechanisms. In recent times, autonomic cortical function has come to be prominently identified with the anterior cingular gyri (area 24). Ample evidence, in subhuman mammals, of autonomic functions of this area have been repeatedly recorded. Tower,[14] Smith,[11,15,16] Ward,[12] Kaada et al.,[17] Dunsmore and Lennox[18] have, during electrical stimulation of the anterior cingular gyrus, observed the following evidences of autonomic discharge: pupillary dilatation, pilo-erection, slowing of the pulse and respiration rates, and variable transient rises or falls of blood pressure. In emphasis of the residence of important autonomic functions in the anterior cingualr gyri (area 24), these areas have been included in what has been termed the "visceral brain,"[5,19] the remaining cortical areas now known to be concerned with visceral function being the orbital gyri (of frontal lobe) and the cortex of the tips of the temporal lobes. As Yakovlev[19] has emphasized, these areas form a closely integrated system which "may be looked upon as a part of the highest representation of visceral function." It is interesting that Nielsen[2] in reviewing the clinical features of cases with callosal-cingulate lesions (Marchiafava's disease) felt that the terminal stage (stage III) might be due to "chest complications" (bronchopneumonia?). In the present case only minimal signs of bronchopneumonia were found on postmortem examination, and it seems more likely from what has already been alluded to that the observations on temperature, pulse and respiration elevations were of neurogenic rather than of pulmonary origin.

SUMMARY

1. The clinical features of a case with postmortem evidence of bilateral lesions of the cingulate gyri (area 24) have been described.

2. The earliest stage is characterized by apathy, akinesia, mutism, urinary incontinence, integrity of deep tendon reflexes, normal muscle tone, open eyes, physiologic pupils, indifference to pain, and bilateral Babinski signs (stage of

"akinetic mutism" of Nielsen[2]), the later stage is characterized by progressively deepening stupor with eventual coma and death ("terminal stage" of Nielsen[2]).

3. It is felt that the symptomatology and clinical course are so characteristic as to constitute a syndrome—the syndrome of the anterior cingulate gyri.

4. The suggestion is made that the disturbances of pulse, respiration and temperature regulation, noted in the present case, may be a reflection of a fundamental derangement in the cortical autonomic regulatory mechanisms heretofore established as being closely associated with the cingulate gyri (area 24).

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It was long ago discovered (by Waller) that if nerve-fibres are destroyed at a given point, they undergo degeneration beyond the lesion, and this degeneration extends along them as far as they continue simple fibres. The degeneration is only in one direction, and that is the direction of functional conduction; on the side of the lesion from which the fibre conducts there is no degeneration. By means of this "secondary degeneration" the course of some tracts of fibres may be traced with precision through the brain.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Potency of Isolated Brachial Dorsal Roots in Controlling Muscular Physiology

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SINCE the beginning of modern neurology, there has been considerable theoretical and practical interest in the possible functions of the sensory roots of the spinal nerves. Pioneers in the experimental field of dorsal rhizotomy include such well known investigators as Bell,[1] Magendie,[2] Claude Bernard[3] and Sherrington and Mott[4] who worked on different species of animals. Clinically, Foerster,[5] Frazier,[6] and Spiller and Frazier[7] were the first to section the posterior roots for therapeutic purposes in man. These fibers have been sectioned for athetosis; for the alleviation of pain produced in angina pectoris, gastric crises, sciatica and cancers; for relieving spasticity in paraplegia and torticollis; and finally for lowering the blood pressure in certain cases of hypertension.

Of the above named investigators, Claude Bernard[3] and Sherrington and Mott[4] focused their attention particularly on motor function. The latter reported that posterior rhizotomy of the roots to the extremities in the monkey causes more serious and enduring deficits than when the motor cortex itself is excised. The results of Lassek[8] harmonize with those of Sherrington and Mott.[4] In order to obtain this effect it is absolutely necessary to section all the involved strands indicating there might be a safety factor in the system.

Some problems in the field of animal behavior include the spontaneity or drive behind motor activities as well as the pattern or coordination of movements.[9] Because there is evidence that the dorsal roots collectively and possibly individually may be important in these categories, it was felt worthwhile to make a study of the role of each one connected to the upper extremity in the monkey.

MATERIAL AND METHODS

The dorsal roots of the left brachial plexus in eight mature monkeys (Macacus mulatta) were cut in such a manner as to isolate one or more of them. Left intact singly in successive animals were either C_5, C_6, C_7, C_8 or T_1, all other dorsal roots being cut from C_2 to T_4. In some, a second operation was performed to note the effect of cutting the remaining root. In addition, C_7

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and C_8 were left untouched in one animal; C_7 and C_8 alone were cut in another, and in the last C_6, C_7 and C_8 were sectioned.

The animals were studied physiologically at frequent intervals postoperatively for periods varying from 22 to 155 days, the average being 84 days. The motor deficits were compared with 12 control animals in which all the brachial dorsal roots had been sectioned. At autopsy, representative sections were taken to study the status of degeneration in the roots and in the ascending sensory pathways, particularly in the posterior columns. In this procedure, silver stains were employed (Protargol and silver nitrate methods).

RESULTS

When either C_6, C_7 or C_8 singly are the only posterior roots linked to an upper extremity, there remains a remarkable ability to perform coordinated and skilled movements. On the other hand, when C_5 or T_1 are the only surviving roots, the motor deficits are near maximal and simulate the marked motor impairment resulting from section of all the brachial roots.[4,8]

Of the five brachial dorsal roots, C_7 seems to be the most important. With this alone intact, it is difficult to discern any interference with voluntary motion immediately following the operation. The animal can climb, eat, grasp and support itself with the involved extremity. Strength and tone remain very near or at normal. After 13 postoperative days, the only abnormality noticed is a slightly lower dropping of the affected extremity when released from an elevated position when compared with the normal. When the isolated C_7 is sectioned 45 days after the first operation, little function remains. The arm becomes flaccid and loose and cannot be used for postural support, eating, climbing or grasping.

The animals with C_6 and C_8 intact are very much the same as the one with C_7, described in the preceding paragraph, except that they are judged to have slightly less strength. This is evidenced by the fact the affected extremities at first fall more as a dead weight when released from an elevated position. The animal with the C_6 dorsal root intact shows recovery in this respect after five weeks, at that time being able to fully check the descending movement. Otherwise, these two animals could climb, grasp, support bodily weight and eat with their affected extremities on the first postoperative day.

When C_5 is the only surviving dorsal root, the muscles of the upper extremity are weak and flaccid. No grasp is present; the arm or hand is used for some postural support but not for climbing or eating. The animal falls heavily as a dead weight from an elevated position. Only slight voluntary motion is noticeable at the shoulder joint, and the involved extremity, on the whole, looks like a typical monkey hemiplegic arm.

The T_1 dorsal root likewise does not have much influence by itself. Following the operation which isolates it, the muscles are weak and flaccid. The upper extremity is not used for support, climbing, grasping or eating and it has no checking reaction. It remains in this condition showing no signs of restitution.

In a monkey with C_7 and C_8 intact, all others being sectioned, the muscles appear to be near normal in function. A neurologic examination shows only the slightest sign of muscular weakness, with a lessened resistance to passive movement. These changes were not in evidence at the end of two weeks. With C_7 and C_8 dorsal roots cut alone in another monkey, the animal is judged to be normal in every way.

In the experiment where C_6, C_7 and C_8 dorsal roots are sectioned leaving C_5 and T_1 untouched, there is initially a marked motor deficit in the upper extremity. In the cage, the affected arm is held against the chest with wrist and fingers in a state of flexion and it is not used at any time. Examination outside of the cage shows little voluntary movement and some resistance to passive movement. At the twelfth postoperative day, the animal grasps with its fingers and uses the arm for support. At the thirty-fifth day, strength in the affected member is increased and it eats with both hands. By the forty-eighth day, the animal appears near normal in its activities in the cage in respect to eating, climbing and support of body weight. A neurologic examination at this time shows that the only deficit is a slight loss of strength. It was sacrificed at the ninety-seventh postoperative day, still showing a minimal loss of strength and weakened grasp reflex.

The postmortem histologic studies made with silver techniques gave evidence that the sectioned dorsal roots were cut completely, whereas the ventral were preserved in all the experimental animals.

DISCUSSION

The possible role of sensation in volition has been discussed comprehensively by Gooddy.[10] He advances the view that sensation and motion form a single, indivisible and continuous process. He believes both that the motor cortex is taught to perform movements by receptors and that no sharp division exists between motor and sensory function. It would be logical to assume that the afferents arising from the muscles, tendons and joints would be important in any teaching of the motor cortex to perform movements and only movements. If Gooddy's overall views could be proved true, then some of our present motor concepts might be reconsidered both from the standpoint of physiology and pathology.

The experimental investigations which have been performed on the dorsal roots of primates, which conduct afferent impulses from the skin and deeper structures including those from the muscles, tendons and joints, show first that a profound and relatively permanent type of paralysis, most pronounced in the distal muscles, develops following section of all the fibers connecting an extremity.[4,8] The present study indicates that a safety factor exists in such a manner that either C_6, C_7 or C_8 singly has almost as much influence on motor physiology as all five brachial dorsal roots acting together. This is especially true of C_7. When it is the only functioning dorsal root, it is difficult to discern any interference with voluntary motor function. C_6 and C_8 rank close behind C_7 in this respect, but C_5 and T_1 individually play a negligible role. The two

together, however, aid in recovering some control over motor activities of an upper extremity.

The greater influence of some of the dorsal roots on motor activity cannot be explained on a quantitative neuronal basis entirely. Larsson[11] reported that there are 222,729 dorsal root fibers in the spinal nerves of the Macaque monkey. This is 2.64 times more than the number of ventral root fibers. The brachial group comprises 65,576, or 29.4 per cent of all posterior roots. Each of these has the following numerical representation according to Larsson[11]:

1. C_5	5,251
2. C_6	11,738
3. C_7	17,711
4. C_8	17,451
5. T_1	13,425
Total	65,576

C_7 has more dorsal root fibers than any of the other 31 spinal nerves. As mentioned, the results of this investigation indicate that it alone can carry on practically the normal motor activities of the upper extremity in the monkey. However, T_1 which has over twice as many dorsal root fibers as C_5 seems to have somewhat less excitatory effect than the latter. Although C_6 has fewer number of fibers than T_1, it has much more influence on motor cells within the central nervous system.

It is difficult to say just how dorsal root impulses may affect the motor cells within the central nervous system and why one brachial dorsal root (C_6, C_7 or C_8) has apparently almost as much physiologic effect as all. The collective impulses coursing over the brachial posterior roots may produce a state of continuous excitation to identical segmental anterior horn cells as well as affect higher suprasegmental motor elements. Preliminary work has been started to determine the possible role of the group of fibers which course up in the posterior columns of the spinal cord as against the influence of the cutaneous impulses originating in the skin and immediate adjacent structures.

It seems permissible to assume, on the basis of this and other investigations on the dorsal roots,[4,8] that pathologic involvement of the sensory pathways within the central nervous system which are synaptically related to the dorsal roots, when extensive enough, may cause deficits in movements, tone and postural adjustment related to voluntary motor functions.

CONCLUSIONS

1. When all the dorsal roots to an upper extremity in the monkey are sectioned a severe, enduring and flaccid type of paralysis immediately ensues.

2. A safety factor seems to exist in the dorsal root system of the brachial plexus, since the seventh cervical dorsal root can exert almost as much motor influence as all the brachial roots collectively. With it alone intact, the animal appears normal in respect to muscular tone, postural support and voluntary movements.

3. The sixth and eighth cervical dorsal roots singly can maintain nearly normal motor function in an upper extremity.

4. The fifth cervical and first thoracic dorsal roots individually exert a negligible influence on voluntary motor control in the muscles of the upper appendage, but the two functioning together permit eventually a considerable degree of movement.

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We speak of nerve-cells and nerve-fibres as if they were merely connected structures, essentially distinct. They are not really so. The axis-cylinder of each nerve-fibre is the prolonged process of a nerve-cell sharing all changes of nutrition that the nerve-cell undergoes, suffering with it when the cell is damaged. This is the secret of the secondary degeneration. If a fibre, or part of a fibre, is cut off from its parent cell, it degenerates; the part still in connection with the cell does not degenerate. If the cell is destroyed, the whole fibre perishes. Although I have said that every fibre is a nerve-cell process, I need hardly tell you that the fact is not proved. It never can be proved by observation. But the relation can be observed of some cells in various parts of the nervous system; the contrary has never been observed; and we may therefore infer, with considerable probability, that the fact is true of all nerve-fibres.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment and to encourage research in therapy of neurologic disorders.

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Barbiturate Intoxication

Fae Y. Tichy, M.D.

SINCE the introduction of the first derivative of barbituric acid for clinical use in 1903, a tremendous amount of literature has accumulated on the barbiturates. The individual clinical, pathologic, pharmacologic and physiologic studies show a remarkable divergence of results and a lack of correlation with one another. Clinically, many contradictions are evident concerning therapeutic applications, toxic effects, and the treatment of barbiturate poisoning. A better understanding of the currently accepted pharmacologic and physiologic effects of these drugs would lead to a more critical and rational attitude in these spheres.

In view of the fact that barbiturates are among the most frequently used and misused drugs in the United States, judged by many authorities as narcotics causing more serious effects than morphine, it behooves the clinician to adopt a more critical attitude concerning the literature on barbiturates and to gain a knowledge of their proper place in therapeutics. The purpose of this presentation is to bring some semblance of completeness and order to the clinical aspects as related to the pertinent literature in the various medical sciences.

PHARMACOLOGIC AND PHYSIOLOGIC ASPECTS

Urea was prepared synthetically by Wöhler in 1828. It is an amido compound and combined with malonic acid it forms malonyl urea or barbituric acid. In 1903 Fischer and von Mering produced diethyl barbituric acid or barbital (whose proprietary name is Veronal). Subsequent investigation indicated that substitution of dissimilar hydrocarbon groups on the side chains produced compounds with preferable clinical effects. In 1911 Hoerlein synthesized phenyl ethyl barbituric acid or phenobarbital (Luminal) which proved to be more potent than barbital with no increase in toxicity. After World War I innumerable modifications of the original compound covered by the German patents were introduced, and hundreds of them have been synthesized during the last 25 years. Amytal was synthesized in

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1921 and introduced in 1923, at which time intravenous and intramuscular use of the barbiturates was also begun. The thiobarbiturate group of drugs was produced by replacing the ketone of urea with sulfur.

As far as usual basic reaction is concerned, these are all very similar in effect; however, differences have been noted in reference to: 1) tendency of some to produce excitement rather than sedative effect in some patients; 2) relative depressant action at the different levels of the central nervous system; 3) variations in time of onset of effect, intensity of effect, and duration and fate of these compounds—some act promptly with a powerful but brief effect and are destroyed rapidly by the body, while others act more slowly, producing a milder effect for longer periods of time and are largely excreted unchanged; 4) variation in therapeutic zone, i.e., the difference between the range of therapeutically effective dosage and the lethal dose. Fitch and Tatum[1] classified the barbiturates on the basis of duration of action into the long, intermediate, short and ultrashort actors, the duration of action being respectively 10 to 15 hours, 6 to 8 hours, 4 to 6 hours, and ½ to 1 hour. McDaniel and Bell[2] suggested three ways of classifying the barbiturates: the first, in order of increasing toxicity: barbital, dional, Dial, Amytal, phenobarbital, and Allonal; the second, in order of increasing efficiency: barbital, phenobarbital, dional, Dial, Amytal, and Allonal; and the third, in order of increasing margin of safety; phenobarbital, barbital, Allonal, Amytal, Dial, and dional.

There are various methods of determining the presence of barbiturates in body fluid and tissues. These include micrography of crystals after ether extraction and recrystallization, gravimetric determinations, melting point studies, cobalt color reaction, and ultraviolet spectrophotometry. Excretion studies done with radioactive barbiturates have also been performed.

The distribution of the barbiturates in the body has been the subject of much investigation. Some have noted the greatest concentration in the brain, particularly in the region of the hypothalamus.[7] However, this particular localization has been strongly questioned and Koppanyi et al.[8,9] found evidence of the drug in the liver, skeletal muscles, and kidneys with a very low concentration in the brain. Analysis of spinal fluid has generally shown only insignificant amounts even after large injections with no relationship to the depressant effects. After intravenous injection, the barbiturates generally remain in the blood only a few minutes and the blood concentration does not correlate with the level of anesthesia.[10] Butler [11] found the depth of anesthesia correlated well with the gradual rise of concentration of barbiturate in the brain. Koppanyi[12] on resuscitating depressed animals with analeptics, found no significant change in the barbiturate content of the blood and organs as compared to controls. Barbiturates also have been recovered from fetal amniotic fluid, bile and saliva. The Martlands[13] found the level of barbiturates in the fetal brain twice that of the maternal brain and demonstrated higher concentrations in the fetal liver, kidney and spleen as well, which they attributed to slow and deficient detoxification and excretion in the fetus.

The fate of the barbiturates varies for the type of barbiturate. They may be excreted almost completely and unchanged in the urine, partly unchanged, or may be completely destroyed in the body. With ordinary therapeutic doses, phenobarbital and barbital are the only ones present in the urine.[5] In large doses most of the barbiturates can be demon-

strated in the urine.[14] Traces of barbital may be found in the urine up to nine days after ingestion and thus a cumulative effect may result; moreover, there is evidence that with habitual use of the barbiturates excretion may be delayed.[5]

Tatum[15] has noted that the thiobarbiturates have very short action since they are rapidly destroyed in the body. He also noted their greater potency and that long continued use may produce a cumulative effect, possibly from some unidentified depressant degradation product. The site of detoxification varies with the type of barbiturates. Most are detoxified chiefly by the liver but barbital and phenobarbital are detoxified chiefly by the kidneys.[3] The kidneys and liver are equally concerned in the detoxification of Dial, Neonal, Phanodorn, and Delvinal.[5]

Innumerable articles have been written about the site of action in the nervous system. The hypothalamus, cerebral cortex, brain stem, or basal nuclei have been favored by various authors but there is no consensus on the site or mechanism of action at present.

The electroencephalographic studies of Brazier and Finesinger[16] on patients given intravenous Amytal, Pentothal and pentobarbital showed the first effect to be that of high-voltage fast activity spreading from the frontal to the parietal and occipital lobes. The second effect, with larger doses, produced slow, three to four per second, delta waves. In the first few minutes of injection, at the stage of maximal action of the drug, the patient might be unconscious without the presence of waves typical of sleep. On arousal high voltage fast activity occurs. Lennox[17] noted that even with small doses of various barbiturates there was an increase in either fast or slow activity, and that there was an increased appearance of abnormalities when the sedatives had been used for days or weeks. Cohn et al.[18] felt the characteristic electroencephalogram of barbiturate intoxication showed random frequency, high voltage waves. Swank and Watson[19] noted that deep narcosis in dogs given Amytal produced marked slowing with amplitude and frequency altered least in the motor areas. They felt that barbiturate narcosis was characterized by periodic decreased spontaneous activity followed by "suppression-burst" phenomenon. In deep narcosis bursts alternating with "blackouts" were produced. Picrotoxin abolished the "blackouts" but when narcosis became very deep, Picrotoxin and Metrazol had no effect.[20]

The mechanism of action of the barbiturates has been studied recently with in vitro and in vivo specimens of the nervous system by chemical analyses. According to Quastel's[21] narcosis theory, the mechanism is that of inhibition of essential enzyme systems of the central nervous system. The precise enzyme systems involved have not been determined although some feel that the anesthetic doses act by inhibition of the pyruvic oxidase system. Using slices of cerebral cortex, a decrease in oxygen consumption can be produced with barbiturates but Grenell and Davis,[22] using local perfusion of brain in vivo, felt there was probably no significant drop in the rate of oxygen consumption with Nembutal in concentrations of the general anesthesia range. Himwich[23] concluded that the two components to narcosis were a decreased oxygen utilization beginning with the phyletically newest levels and spreading down the neuraxis and an impairment of nerve activity with elevation of synaptic threshold.

Although it is generally denied that the barbiturates have an analgesic effect, Keats and Bucher[24] felt they could attain analgesia with hypnotic amounts of pen-

tobarbital given intravenously to patients with postoperative pain.

Another factor important in the mechanism of action is that barbiturates do not cause depression of the nervous system in all patients. Some react to the usual sedative doses with excitement, delirium and hallucinations and others show marked hypersensitivity and even develop profound coma. There are also variable delay reactions to intravenous injection. The presence of other drugs or of pathologic states markedly alter the effects of the barbiturate. There appears to be a synergistic or summation effect with nitrous oxide and cyclopropane. The barbiturate effect may be increased by calcium, alcohol and morphine. The use of barbiturates to control the central stimulatory effect of cocaine intoxication increases the possibility of respiratory failure.[25] In patients suffering from therapeutic hyperinsulinism and treated with Amytal, the prolonged coma suggested the possibility of synergism between insulin and Amytal.[26] Yannett[27] noted that the cerebral changes from insulin and pentobarbital were much more severe than from insulin alone. However, many advocate Amytal interviews during the immediate postinsulin period in treating psychoses.

Since the liver and kidneys are concerned in detoxification of the various barbiturates, damage to these structures will alter the expected clinical effect. Many authors have indicated that liver damage will prolong the effect of the short acting barbiturates, and they warn against the use of these drugs where liver damage is present. Renal failure increases the susceptibility to the effect of Amytal, phenobarbital and pentobarbital. Hyperthyroidism is also considered a contraindication to the use of Amytal.[28] It has been noted that old or castrated animals are more susceptible to the short actors, possibly because of the influence of the sex hormones on liver metabolism.[29]

The effects of therapeutic doses of the barbiturates on respiration and circulation also merit consideration. During anesthesia with certain barbiturates, episodes of coughing, hiccupping and serious laryngospasms may develop which have been attributed to central vagal stimulation and to release of control by higher centers. If large amounts of any barbiturate are injected rapidly intravenously death results due to paralysis of the respiratory center or to temporary flocculation of the sparingly soluble acid.[5] Thiobarbiturates may cause cardiac irregularities and Gruber[3] felt that these might be contraindicated in patients taking digitalis.

CLINICAL ASPECTS

Frequency of use of barbiturates. The barbiturates are the most widely used of all sedative and hypnotic drugs. Although several of the early workers reported on the habit-forming nature of the barbiturates, statistical proof was not furnished until 1940 when Hambourger[6] published his astonishing report on the promiscuous use of the barbiturates in the United States. He found that one of every nine addictions involved the use of barbiturates and that the reasons for the addictions were listed as 1) sedation, 2) substitution for alcohol, 3) nervousness, and 4) epilepsy. He noted that psychopathic personalities and morphine addicts were particularly prone to the barbiturate habit. Two-thirds of 85 addicts said they had become familiar with the drugs through a physician. Since this report, numerous others have been published, indicating an appalling increase in death rate and addictions to the barbiturates. At present the drug is the most popular agent in suicide attempts.[30] Robie[31] noted a 677 per cent increase in death rate from barbiturates

between 1944 and 1947 in Los Angeles. In 1950 the production of barbiturates exceeded that needed for therapeutic use. Isbell and Fraser[32] felt that barbiturate addiction represented a true addiction of a more serious nature than morphine addiction, yet the literature continues to be filled wjth numerous articles acclaiming the merits of the barbiturates for therapy in conditions which could be more safely alleviated by other means. Currently it is being used to treat alcoholics and many do not realize that they are substituting a much more dangerous drug for alcohol in these patients.

Acute barbiturate intoxication. Acute barbiturate intoxication usually results from ingestion of a single large dose either accidentally or with suicidal intent. The individual variation in the response to various doses of barbiturates precludes making definite statements about the minimal lethal dose and the maximal non-fatal dose. Wilcox,[33] for instance, noted that patients consuming 50 to 125 grains of barbital usually recovered but some with idiosyncrasies might succumb to as little as 10 grains. After oral ingestion of a large amount of any barbiturate, the patient first appears drowsy, slightly confused, ataxic, and exhibits occasional muscle twitchings. He often complains of headaches or dizziness and gradually becomes comatose or delirious. In deep coma there is suppression of deep reflexes and general muscular flaccidity; there may be positive Babinski signs and evidence of focal involvement. The pupils may be dilated or constricted and occasionally exhibit hippus. Respiration is usually shallow and may be of the Cheyne-Stokes or Kussmaul variety. In deep coma the pulse is slow, the blood pressure decreased, even to shock level, and the skin is cold and cyanotic. If the patient recovers, he usually regains consciousness in 24 to 48 hours; however, cases have been reported that survived after two to three weeks of coma. As the patient recovers, evidence of ataxia, nystagmus, ptosis of the eyelids, slurred speech, or diplopia may become apparent. The nystagmus, in particular, may persist for months and the patient may remain slightly euphoric, irritable, agitated and negativistic for long periods of time. Patients may also appear to improve with the return of consciousness and then subsequently expire with or without again becoming comatose from the effects of pulmonary edema and congestion, gradual heart failure, or pneumonia.[34]

Many unusual clinical conditions have resulted from acute intoxication with the barbiturates. Generalized spasticity, rigidity, tonic neck reflexes, motor quadriplegia, athetosis, severe mental confusion, peripheral neuritis and gangrene, transient xanthopia, disturbances in color perception, conjunctivitis, and photophobia, convulsions, vascular insufficiency with orthostatic hypotension, and "cerebral edema" with urticaria, angioneurotic edema, papilledema, and increased cerebrospinal fluid pressure have been reported as secondary to episodes of acute barbiturism.

Numerous findings have been reported during acute intoxications which resemble other central nervous system diseases and pose a difficult problem in differential diagnosis. Acute intoxications have been reported simulating epidemic encephalitis, multiple sclerosis, syringomyelia, tabes, tetany, delirium tremens, and cerebellar and midbrain syndromes. Increased toxic effects were noted particularly in patients with renal disease, poor liver function, and states of oxygen deficiency (anemia, bronchitis, kyphoscoliosis, or advanced pulmonary disease). Scarlett and McNabb[35] added senility, debility, arteriosclerosis,

hypertension, myocardial disease, and severe toxemias from sepsis as definite contraindications to the use of the barbiturates. Hoaglund[36] warned that barbiturates may precipitate but not cause episodes of acute porphyria.

Chronic intoxication. As early as 1905 toxic symptoms were reported from barbital. During the next 20 years numerous reports were published in reference to the symptoms, including drowsiness, ataxia, tremor, slurred and scanning speech, and gastrointestinal disturbances. Work,[37] in 1928, warned that the prognosis should be guarded as to restoration of psychic faculties and described two patients with chronic barbiturate poisoning who had persistence of severe mental symptoms on withdrawal.

Chronic intoxication results from prolonged ingestion with a cumulative effect. A simple intoxication is usually transitory and the patient shows signs of drowsiness and occasional excitement such as noted in elderly patients on small doses of the barbiturates. This type usually is completely gone within six to 24 hours. Other patients seem to have a natural idiosyncrasy to the drug and react with repeated episodes of excitement similar to a state of inebriation, or accentuation of their pre-existing emotional disturbances may be noted. Many of this group exhibit "hangovers" with lassitude, vertigo, gastrointestinal disturbances, and localized or diffuse pain of a myalgic, neuralgic or arthritic type. These complaints are usually more intense in the morning and may persist several days after discontinuation of the drug. Intolerance may develop in a patient who previously tolerated the drug well.

The more common findings in chronic barbiturate intoxication are profound psychiatric disturbances with marked emotional instability, either euphoria or depression, defect in attention, comprehension and judgment, dulling of ethical sense, mild somnolence and confusion, periods of amnesia, motor restlessness (especially at night), and occasionally acute toxic delirium. Neurologic signs and symptoms include tremor, nystagmus, irregular or unequal pupils, ptosis of the eyelids, diplopia, defects of speech of drawling, scanning, or incoherent types, and reflex changes, consisting of either decrease or increase of deep reflexes and absent abdominal reflexes. The patient may complain of dizziness, weakness of the legs, and chronic pains and paresthesias. Occasional patients also complain of general malaise with nausea, colicky epigastric pain, constipation, mild fever, coryza and dermatitis. Many authors have described cutaneous lesions as being common in chronic poisoning and due to acquired idiosyncrasy. Exfoliative dermatitis due to phenobarbital has been noted as well as hepatitis and jaundice.

Many authors have noted the increase in seizures in epileptics on withdrawal of barbiturates. The withdrawal symptoms in chronic addicts include convulsions and/or a psychosis. The psychosis is of the delirious type and usually clears rapidly on beginning the drug again. In 1950 Isbell et al.[38] published the results of their clinical experiments with chronic barbiturate intoxications induced in five former morphine addicts by giving them doses of Seconal or Amytal sufficient to cause continuous, mild or severe intoxication for 92 to 144 days. Their report is worthy of special consideration. During the period of chronic intoxication, there were marked changes including impaired mental ability with confusion, regression, increased emotional instability, and definite evidence of deterioration on psychometric studies as well as nystagmus, dysarthria, ataxia, decreased abdominal reflexes, and Babinski signs. Some tolerance developed consisting

mostly of decreased sleeping time. A cumulative effect was noted even with the short actors. On abrupt withdrawal, a definite abstinence syndrome developed similar to alcoholic delirium tremens. Grand mal seizures usually developed from 16 hours to five days after withdrawal. Usually only three seizures were noted but the authors indicated that 100 or more such seizures had been seen as well as minor seizures and athetosis. The psychoses usually began three to seven days after withdrawal. Recovery appeared to be complete in that there was no clinical evidence of permanent damage, with both psychometric and encephalographic tracings returning to their previous pattern. The authors concluded that barbiturates are addiction-forming drugs and in some respects addiction to barbiturates is more dangerous and undesirable than addiction to morphine, since morphine generally causes less impairment of mental ability and emotional control and causes no motor incoordination. Withdrawal from morphine is also less dangerous.

Treatment of barbiturate intoxication. There is no known antidote for barbiturates and most of the therapy of acute barbiturate poisoning has revolved about the use of one or more of the large groups of analeptic drugs. Eckenhoff et al.[39] divided the analeptics into four groups: 1) those whose primary stimulation action is on the nervous system (Picrotoxin, Metrazol, nikethamide, strychnine, caffeine, and atropine, the last three of which were regarded as useless for analeptic purposes); 2) those which mediate analeptic effects through reflexes such as the carotid and aortic bodies (alpha lobeline, cyanides, sulfides, nicotine, smelling salts, aromatic spirits of ammonia, whiskey, brandy, subcutaneous camphor, alcohol, or ether); 3) drugs stimulating both central nervous system and cardiovascular system and which may cause not only convulsions but also hypertension and tachycardia (Benzedrine, Dexedrine, and Methedrine); 4) substances causing a specific stimulant effect on nerve tissue by entering directly into biochemical reactions on which the excitability of this tissue depends (pyruvate, succinate, fumarate, and vitamin B). The authors indicated that the mechanism of action of analeptics on narcotic depression was most probably a physiologic antagonism. They concluded that Picrotoxin and Metrazol were the most valuable analeptics, Picrotoxin being the more potent but also the more dangerous, and indicated that it should be used only for deep depressions. Picrotoxin produced convulsions if given more frequently than every 30 minutes because of its prolonged action. Metrazol attained its maximal effect immediately after injection and thus might be valuable in treatment of respiratory depression due to shock and ultrashort-acting barbiturates. Nikethamide, caffeine and strychnine were found to be relatively useless as analeptics. They felt that the only justification for the use of succinate was that overdosage was not associated with convulsions. Many papers in the literature favored drugs which were found by these authors to be completely useless and often dangerous.

Koppanyi and Fazekas[40] suggested that the best indication for the use of analeptics in comatose patients with barbiturate intoxication was the response to one intravenous injection of 5 cc. of 10 per cent Metrazol. If response was good, only symptomatic care was indicated. If there was no response, they felt Picrotoxin would have definite life-saving value for long-acting barbiturates or massive doses. Picrotoxin should be given in 1 mg. to 3 mg. doses every 30 minutes until the reappearance of corneal, swallowing, or other reflexes, or

TABLE 1

	Hypnotic dose (in grams)	*Sedative dose* (in grams)	*Minimal fatal dose* (in grams)	*Maximal non-fatal dose* (in grams)
Long:				
Phenobarbital (Luminal)	0.03	0.015 to 0.1	1.6	9.1
Barbital (Veronal)	0.5	0.1 to 0.15	2.0	32.5
Intermediate:				
Neonal	0.05 to 0.1			
Dial	0.1 to 0.3			2.4
Ipral	0.12 to 0.25			
Alurate	0.06 to 0.13			
Nostal	0.1 to 0.3			
Amytal	0.1 to 0.3	0.02 to 0.04	1.6	7.2
Sandoptal	0.2 to 0.4			
Short:				
Pentobarbital (Nembutal)	0.1 to 0.2			1.0
Phanodorn	0.1 to 0.2			
Ortal	0.2 to 0.4			
Ultra-short:				
Evipal				
Thioethylamyl				
Thiopentobarbital (Pentothal)				

Classification of barbiturates by Fitch and Tatum as modified by Gruber.[3] In addition, the hypnotic dose[4] and the sedative dose as well as the minimal fatal and maximal surviving dose are noted for some of the most commonly used barbiturates.[5,6] As a rule, the fatal dose varies from 15 to 30 times the therapeutic dose.

until there is evidence of twitching of the facial muscles according to Burdick and Rovenstine.[41] Metrazol is preferred by many for treating intoxication with the shorter actors.

In 1950, Robie[42] noted that while using minimal dosage unidirectional electric stimulation for "psychostimulation" on psychotic patients, the patients who had been sedated with Pentothal awakened. He tried this effect clinically on acute barbiturate poisoning with excellent results. He found it required only a few minutes stimulation with only a few milliamperes current to awaken even deeply comatose patients.

The general therapeutic program for the deeply comatose patients should also include: 1) establishment of an adequate airway; 2) intravenous fluids in large doses but with consideration of the possibility of precipitating pulmonary edema or cardiac failure; 3) indwelling catheter if needed; 4) oxygen as indicated with 10 per cent carbon dioxide; 5) cardiac and respiratory stimulants may be needed in cases which show evidence of shock; 6) antibiotics, turning the patient every 30 minutes, frequent pharyngeal suction, and keeping the patient warm to avoid the chief complication of barbiturate intoxication, pneumonia. Gastric lavage is contraindicated because of the danger of aspiration.

Treatment of the patient with chronic barbiturate intoxication or addiction consists of a gradual reduction of the drug to prevent any evidence of the abstinence syndrome.

SUMMARY

A review of the clinical aspects of barbiturate intoxication as well as the pertinent pharmacologic and physiologic

aspects are presented to point up the dangers involved and the need for a more judicious and limited use of barbiturates.

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Excitement in the cerebral system may be much diminished by a due attention to seclude the patient from the light, from noise, from every kind of mental disturbance. To this branch of our subject belongs to the whole of the *moral* treatment of the insane, as it has been termed.

In reference to the true spinal or excito-motory system, much more may be done.

Strychnine obviously excites this system; whilst the hydrocyanic acid as obviously diminishes its powers. These two remedies may, therefore, have appropriate applications. But I have seen them sadly misapplied. What do you think for instance, of strychnine as a remedy for hydrophobia? Would you not as soon give the hydrocyanic acid in the paralysis of colica pictonum?

The carbonate of iron and the liquor arsenici are other remedies, the powers of which are only partially explored. They cure chorea.

Then we have an important remedy in electricity and galvanism. Have its powers been *appropriately* applied?

Another important remedy, in the class of true spinal affections, is the dashing of cold water on the face, or surface. This remedy tends to open the larynx in epilepsy, and to convert the violent *expiratory* struggles into acts of inspiration.

Another agent which has great influence upon the excito-motory system is change of air: this is observed in the later stages of pertussis, the croup-like convulsion, &c.

—Marshall Hall in *Lectures on the Nervous System and its Diseases*, published in 1876.

CLINICAL PATHOLOGIC CONFERENCE

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CASE PRESENTATION

A 20 months old female infant was admitted to the pediatrics service because of convulsions. Except for frequent upper respiratory infections the child had been well until two weeks prior to admission when she developed a "cold," with coryza, cough, anorexia and increasing irritability. Five days prior to admission she seemed more irritable and, alarmed at her failure to improve, the family called a physician who gave her some medicine which had little effect. Two days prior to admission she started to vomit. On the day of admission she had a series of generalized convulsions and was brought to the hospital.

Past history: The mother's pregnancy and labor and the infant's postnatal period were normal. There was no known exposure to infectious diseases. For five months prior to admission the child had been nibbling at the window-sills of the house in which she lived.

Family history: Four older siblings were in good health.

Physical examination: Temperature 98° F.; blood pressure 115/60; pulse and respirations normal on admission. The skin was pale and dry. The tongue was coated. The tonsils were enlarged and injected. There were enlarged non-tender axillary lymph nodes. Inspiratory and expiratory rhonchi filled both lung fields. A sinus arrythmia was present, but the heart was not enlarged and no murmurs were heard. The liver and spleen were palpable just below the costal margins. There were frequent generalized convulsions.

Hospital course: The child was started on intramuscular penicillin, 50,000 units every three hours. On the second hospital day, breathing was labored, and there was no response to painful stimuli. Frequent convulsions lasting 30 to 60 seconds continued through the day, although they became less frequent after administration of magnesium sulfate and phenobarbital. On the third hospital day her temperature rose to 104° F. Because one acid-fast bacillus was found in the first cerebrospinal fluid smear, intramuscular as well as intrathecal Streptomycin was begun. Generalized convulsions ceased on the fourth hospital day, but the state of unresponsiveness continued. Twitchings of the mouth were first noted on the sixth hospital day and involved the facial muscles bilaterally on the eighth hospital day. By the ninth hospital day there were constant irregular twitchings of the muscles of the left face, arm and leg, but for the first time she began to take fluids by mouth. On the twelfth hospital day she became cold and clammy, the pulse grew weak, the blood pressure was unobtainable, and it was noted that the arms and legs were very stiff in extension. On the thirteenth hospital day (four weeks after onset of the present illness), the child became cyanotic and died soon thereafter.

TABLE 1

LABORATORY STUDIES

Urine:	*Hosp. Day*	*Sugar*	*Albumin*	*Acetone*	*Sediment*
	2nd	2+	—	4+	—
	3rd	1–4+	—	2+	—
	7th	3+	v.s.t.	0	—
	8th	3+	s.p.t.	0	15–30 WBC
	11th	1+	0	0	20–40 WBC

Color: yellow; reaction: acid; positive for porphyrins.

Blood:	*Day*	*Hemoglobin*	*RBC*	*WBC*	*Smear*
	3rd	75%	4.5 m.	15.2	56P, 44L, 3–5 stippled RBC/Hpf
	13th	65%	3.9 m.	34.6	79P, 19L, 1M, 3–5 stippled RBC/Hpf

Chemistry:

a) Blood Sugar
2nd day 175 mg. per 100 cc. (fell to 30 mg. per 100 cc. after insulin)

b) Carbon Dioxide Combining Power
2nd day 25 volumes per cent
3rd day 45 volumes per cent

Spinal Fluid:

Hosp. Day	*Total Cells*	*Cell-Differential* P	L	Monos.	(mg.%) *Protein*	(mg.%) *Sugar*	(mg.% as NaCl) *Chlorides*
3rd	58	21	17	20	69	47	670
4th	27	12	9	6	—	—	—
4th	60	20	20	20	—	56	715
6th	55	40	10	5	63	105	
7th	137	96	24	17	—	—	
9th	22	6	10	6	333	53	
11th	10	0	9	1	—	—	

"One acid-fast organism" reported in fluid of 3rd day; no fibrin-clot; no xanthochromia; all other smears and cultures negative.

CLINICAL DISCUSSION

DR. KANE: Despite the absence of certain important data, I believe we can now proceed to a critical analysis of the problems presented by this patient. Since it seems reasonably clear that the child was suffering from central nervous system disease, our approach to the correct diagnosis will depend on the answers to the following questions: 1. *What part or parts of the nervous system were involved?* We are dealing here with diffuse intracranial disease associated with a meningeal reaction in the spinal fluid. This may turn out to be more marked on the right side because of the report that constant twitching was more marked on the left side of the body. In the absence of information concerning pressure readings on the spinal fluid, diastasis of the sutures of the skull, "cracked-pot" sign, or choked discs, we are not entitled to guess as to the presence or absence of increased intracranial tension. The final episode with extensor posture, however, strongly suggests a decerebrate state following an acute increase in intracranial pressure. The usual mechanism of this involves herniation of the medial temporal lobe (unilaterally or bilaterally) through the tentorium cerebelli with compression, distortion, and hemorrhage in the rostral brain-stem. Herniation of the tonsils of the cerebellum may occur, but is much less common in these circumstances. 2. *Was the cerebral disease congenital or acquired?* The negative past history would lead me to the latter conclusion. 3. *Was the disease-process primary or secondary within the nervous*

system? This will be discussed later; at this point, I believe I would favor the latter.

In essence, we are presented with the problem of a subacute, initially afebrile illness associated with coma and generalized convulsions and an abnormal spinal fluid, mild anemia, leukocytosis, stippled red blood cells, glycosuria, porphyrinuria and, possibly, hypertension in a previously healthy 20 months old female infant.

I am reasonably certain that there are only two possibilities deserving of serious consideration in this case: a) *tuberculous meningitis;* and b) *lead-poisoning with encephalopathy.* The former was obviously seriously considered on the ward as witnessed by the institution of intrathecal Streptomycin. Apart from the blood findings, the cerebrospinal fluid would be compatible with this diagnosis except that the glucose content in tuberculous meningitis usually averages between 20 and 40 mg. per 100 ml. (and may be lower terminally). I am not impressed with the values for chloride in this case. Frequently cerebrospinal fluid chloride in tuberculous meningitis may be as low as 520-610 mg. per 100 ml. (normal: 700-750 mg. /100 ml. as NaCl) or even lower, but it is well known that this reduction is quite nonspecific. Despite the "one acid-fast organism" said to have been seen in the first spinal fluid examination, there was no proof of infection and no history of infectious exposure. Since there is a paucity of positive evidence for tuberculous meningitis and much more data in favor of lead encephalopathy, the latter is much the better possibility. It is of considerable interest that in industrial medicine the concept that lead-poisoning enhances the likelihood of pulmonary tuberculosis is still widely accepted.

Two or more of the following criteria are regarded[1,2] as essential in the diagnosis of lead poisoning: a) a history of exposure to lead; b) a mild to moderate anemia, often with leucocytosis; c) stippling of the red blood cells (9000/million); d) a characteristic "lead-line" at the ends of the long bones; e) lead determinations as follows:

Urinary concentration in excess of 0.2 mg./liter.
Fecal concentration in excess of 1 mg. daily.
Blood concentration in excess of 0.1 mg. per 100 ml.
Porphyrinuria and glycosuria may occur.

One rarely finds a "lead-line" on the gums of children, nor is there always a history of colic. It is apparent that the diagnosis must rest on the composite picture.

According to Weller and Christensen[3] the spinal fluid is characteristically clear, sterile and colorless, under increased pressure, with increased cell count (usually mononuclears), mild to moderate increased protein, normal or slightly increased sugar content, and negative Wassermann. It is not commonly recognized that polymorphonuclear cells may be found in the acute, severe case. The cerebrospinal fluid findings in the present case are therefore fully consistent with the presence of a fulminating type of lead encephalopathy. The rapid evolution of the encephalopathy and the later cell count in the spinal fluid would be completely atypical for tuberculous meningitis.

The danger to small children from lead encephalopathy has been recognized only in the past three decades. The mortality in several reported series of the more severe type of this syndrome ranges from 25 to 66 per cent.[4–6] Byers and Lord[7] have emphasized the deleterious late effects of excess lead on mental development, scholastic attainment and personality. In the vast majority of these instances, as in the patient under discussion, the source of poisoning was lead

paint chewed or nibbled about the house. Thirty cases have been diagnosed at the Children's Medical Center in Boston in the last decade so that it still represents a statistically significant problem.

I conclude, therefore, that the diagnostic criteria of lead poisoning are fulfilled in this case and that the cerebrospinal fluid findings are also consistent with this diagnosis. The fulminant course might be attributed to the fever accompanying the "cold" preceding final illness. Convulsions are characteristic and increased intracranial pressure is well known.

I was unable to discover whether the convulsions in reported cases are possibly related to hypocalcemia. I hope Dr. Foley will be able to tell us why this condition is so much more common in children than in adults, who usually develop a peripheral neuropathy. We will also be interested in his formulation of the basic neuropathologic lesion and in the cause of the acute hydrocephalus seen in these children.

CLINICAL DIAGNOSIS

1. Acute encephalopathy with meningeal reaction in the spinal fluid and anemia due to lead poisoning.

2. Probable terminal pressure-cone formation, secondary to acute brain swelling.

PATHOLOGIC DISCUSSION

DR. FOLEY: Dr. Kane's conclusion that this patient died from lead poisoning with lead encephalopathy is entirely consistent with the findings at autopsy. There was no evidence of tuberculosis or other infectious process in any of the organs.

The significant gross pathologic findings outside the central nervous system were congestion and edema of both lungs, agonal intussusceptions of the small intestine, and two ulcerations of the first portion of the duodenum. Microscopically, these duodenal lesions consisted of areas of denuded mucosa, with an inflammatory round cell reaction at the base.

The scalp, skull and dura mater were normal. The cranial venous sinuses were patent. The paranasal sinuses showed no infection. The brain was under increased pressure and was generally pale and firm. There were herniations of both temporal lobes anteriorly and posteriorly through the tentorial openings, as well as a subfalcial herniation from right to left. A slight degree of cerebellar coning into the foramen magnum was also present. The herniated portions of the temporal lobes were softened and discolored (figure 1). There were bilateral hemorrhagic infarctions in the territories of the posterior cerebral arteries, presumed to be due to compression of these vessels at the incisura. No other areas of occlusion were demonstrated in the arteries at the base.

The brain was cut in coronal section. There was marked edema of both the gray and white matter. In addition to the necrotic areas in the distribution of the posterior cerebral arteries, there was a linear band of hemorrhagic infarction in the anterior portion of the left internal capsule and another zone of hemorrhagic infarction which involved the lateral nucleus of the left thalamus. The midbrain and upper pons were distorted and compressed, but no softenings were found.

On microscopic examination the infarcted areas gave evidence of a process of no more than three to five days' duration. There was loss of many nerve cells, ischemic change in others, with an outpouring of polymorphonuclear leucocytes from the walls of the smaller vessels. There were a few polymorphonuclear leucocytes in the lepto meninges overlying these areas. Obviously they could not account for the polymor-

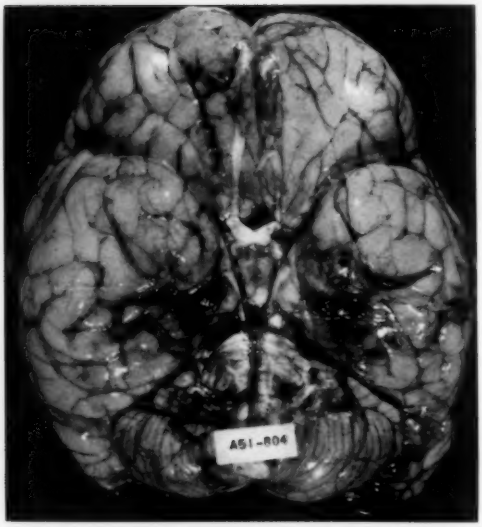

FIG. 1. Swollen, pale brain. Bilateral tentorial herniations. Hemorrhagic infarction in the distribution of both posterior cerebral arteries.

phonuclear cells found in the lumbar puncture done earlier in the course of the illness.

Outside of the areas of necrosis, there were changes seen in all sections studied from many areas of brain. These changes were entirely consistent with lead encephalopathy. There were lymphocytes and mononuclear cells in the subarachnoid space (figure 2), but except in the areas of infarct necrosis no polymorphonuclear leucocytes were seen. The most important lesions were in the smaller blood vessels of which there was an apparent numerical increase. It has been pointed out by others that this increase is more apparent than real. Certainly, the vessels in this case assumed an increased prominence because of a thickening of their walls and a clear space surrounding them. The thickening of the vessels was due to a proliferation of endothelium, which was especially pronounced in the capillaries. No necrosis or occlusion of vessels was demonstrated.

Throughout both gray and white matter, but most pronounced in the cerebral cortex, there were foci in which the tissue had a spongy appearance. The cellular inflammatory reaction in these foci was variable, but usually the nerve cells were lost and some microglial activation was present. Sometimes these foci had blood vessels in their center but this was not a consistent finding.

The principal morphologic abnormality in lead encephalopathy would appear to be an alteration in the smaller blood vessels. This produces an increase in permeability and multiple zones of ischemic necrosis. These effects are widespread throughout the brain, and the extensive damage explains why recovery in terms of life or normal mental function is so rare.

The alteration in the blood vessels, with edema and asymmetrical infarction, would appear to be a sufficient cause for the asymmetrical increase in intracranial pressure which produced the tentorial herniations and probable decerebration in this case. The condition is

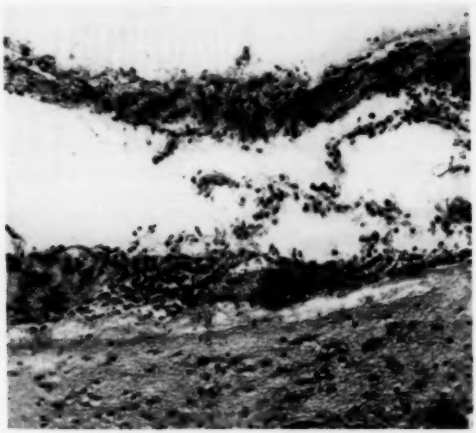

FIG. 2. Lymphocytes, histiocytes, and macrophages in the subarachnoid space at the base.

acute brain swelling and not hydrocephalus.

However, there are many things about lead encephalopathy which morphology alone cannot explain. It is not unusual for the symptoms to appear following an infection, as in this case. Lead encephalopathy is very rare in the adult, even when there is lead colic and peripheral neuritis to give evidence of dissemination of the toxin. It is well known that children develop acidosis easily in the course of an infection. Acidosis, of course, tends to mobilize stored lead. Children, also, are subject to rapid fluid shifts in brain and develop cerebral edema from a multitude of toxic and infective causes. This liability to acidosis and facile cerebral fluid shifts, together with the susceptibility of young cells to lead, may explain why lead encephalopathy is so frequent in young children.

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Neurology BOOK REVIEWS

Diseases of the Nervous System in Infancy, Childhood and Adolescence

Frank R. Ford, M.D. Third edition. 1952. Springfield: Charles C Thomas, Publisher. 1181 pages, $18.50.

The third edition of this well known text on pediatric neurology has been enlarged and revised. It is well bound, well printed, and the illustrations are nicely reproduced. The text is logically arranged and smoothly written. It covers the entire complex field of disorders of the nervous system in infancy, childhood and adolescence. The table of contents is made up of an unusually full outline which, added to the lengthy index and excellent bibliographies for each section, makes this a very usable and useful reference book for physicians and students.

The first chapter is devoted to "The Examination of the Nervous System" and the second to "Clinical Aspects of the Anatomy and Physiology of the Nervous System." Some sections of Chapter I are somewhat more detailed than might be necessary and others are too sketchy. Chapter II, however, is unusually well written and from the point of view of applied neuroanatomy and neurophysiology it is a textbook in itself and should be required reading for every student of neurology. There are few other places, if any, where a more lucid, readable description of the basis of normal and abnormal neurologic signs can be found.

In the remaining chapters the extensive subject matter is logically presented. All aspects are covered. The author's wide experience makes the chapters on prenatal and developmental defects and heredofamilial and degenerative diseases particularly good. However, it is manifestly impossible for any one individual to become familiar in experience with all disorders of the nervous system. Consequently, the author depends on the published observations of others for discussions of many rare and unusual conditions. Not all of the sections on treatment have been brought abreast with the emphasis given in current literature, as for example, the recommendation of plaster immobilization in acute poliomyelitis, and the discussion of metal chemotherapy before penicillin in neurosyphilis. Arteriography is not given prominence. But these are small items. This book continues to be an important contribution to neurology and it should be familiar to all in the field, even though not concerned with pediatrics in practice.

A. S. R.

Introduction to Clinical Neurology

Gordon Holmes, M.D. Second edition. 1952. Baltimore: Williams and Wilkins Company, 189 pages, $4.00.

This small volume, as its name implies, is a text book for medical students who are engaged in the study of clinical neurology. Its avowed purpose is to help the student integrate symptoms of disease with functional and structural

involvement of the nervous system. Thus, it is essentially a text of neurophysiology and like most texts for clinical use, it has lagged behind the published productions of the experimental workers. This is especially patent in the chapters dealing with the motor system. In explaining spasticity and abnormal movements, the author speaks repeatedly of release and inhibition indicating a release of a system normally held in check by another. He fails to give recognition to certain researches indicating pathways, stimulation of which gives rise to motor activity above and beyond that which would occur if the inhibitory influence of a damaged pathway were removed. He does not seem impressed with the cortical representation of these inhibitory and facilitory (extra pyramidal) systems nor the continuity of such systems. He does indicate his dissatisfaction with some of the orthodox theories he supports in relation to spasticity for he refers to the varying disposition of hypertonus. Yet he fails to take advantage of the newer knowledge of cortical localization and projection to explain the clinical pictures that the neurologist sees. He refers to the divergence in numbers of cells destroyed in the precentral motor cortex and number of degenerated fibers in the pyramidal system, but fails to take advantage of the publication of other localizations of motor areas. There is no reference to supplementary or secondary motor areas; nor to suppressor systems having cortical representation in areas 4, 8, 2, and 19.

One can well appreciate the difficulty of integrating all the recent developments in neurophysiology with clinical symptomatology, but that does not excuse neglecting the existence of new knowledge and failing to suggest the possibility that in the near future neurologists will be better equipped to explain the basis for the unending variety of neurologic syndromes.

The weakness in teaching of clinical neurology is in part due to a lack of knowledge in basic neurophysiology on the part of the clinical neurologist. The student comes into clinical neurology with a knowledge of structural anatomy (as much as he remembers from a course given in the first year of medicine) but he is lacking in understanding of the functional activity of the nervous system. Such a text as Holmes offers could satisfy a need to bridge the gap, and while the Holmes text is a step in that direction and is very good in some areas, is does not completely satisfy the reviewer.

M. G. M.

Diagnostic Electroencephalography

Hans Strauss, M.D., Mortimer Ostow, M.D. and Louis Greenstein, M.D. 1952. New York: Greene & Stratton, 282 pages, $7.75.

Strauss, Ostow and Greenstein present this volume, drawn from their material at Mt. Sinai Hospital in New York. They hope it will serve to decrease the amount of oral instruction necessary for the training of clinical electroencephalographers and to acquaint physicians with the field who are not planning to become electroencephalographers. Part I, General Aspects of the Electroencephalogram, deals with the normal EEG, techniques, artifacts, physiology and its abnormalities of wave shape frequency and dyssymmetry.

Part II deals with the electroencephalogram in disease. This is the largest section of the book and presents the results the authors obtained and some correlation with the findings of other investigators.

Part III, the Diagnostic Evaluation, includes a comprehensive table of the pathologic diagnoses of the patients on whom EEG's were performed, and a di-

vision of pathologic entities into the number and percentage of patients in each category who have normal EEG's. These three parts comprise 168 pages of text and are followed by a 17 page bibliography of the field of encephalography. The last 89 pages of the book are illustrations of electroencephalographic records.

There are certain minor complaints which might be raised. The authors, by maintaining their own alphabetical coding of description records, sometimes make it difficult for others not accustomed to these systems. The location of the illustrations at the end of the book necessitates considerable thumbing from text to illustrations. The illustrations present various artifacts, normal and pathologic type of records. Except for the records of normal children, the clinical picture is not indicated below the record.

This book would not suffice for the basic training of an electroencephalographer. It is useful as an entry into the field, but probably its best function will be to acquaint doctors, either in neurology or in other fields, who need some acquaintance with the field of electroencephalography.

F. M. F.

The History and Development of Neurological Surgery

Ernest Sachs, M.D. (Foreword by John F. Fulton, M.D.). 1952. New York: Paul B. Hoeber, Inc. 158 pages, $5.00.

This history of neurological surgery, written by one of the early specialists in the field, follows the development of surgical techniques through the ages, with particular emphasis on the advances of the last 50 years.

In the first chapter the practices of the neolithic, early Egyptian and Greek races are deduced from the neolithic skulls found in Europe and the few extant writings of the ancients. The advances in cranial surgery of the Greek and Roman periods are described in the next chapter with particular reference to the writings of Hippocrates and Galen. The third chapter follows the decline of surgery in the Arabian period and is renaissance in Italian and French surgery of the fifteenth and sixteenth centuries. The fluctuations in surgical practice in the seventeenth and eighteenth centuries due to a lack of fundamental knowledge of neuropathology are illustrated by the controversy which developed at this time over trephining skull fractures. In the Listerian era the roots of modern neurological surgery may be found; from this period Dr. Sachs traces the evolution of the treatment of head injuries, brain tumors, convulsive disorders, neuralgia, peripheral nerve lesions and infections. In the final chapter on modern neurological surgery, the developments in operative technique in the past 25 years and the maturation of the specialty are skillfully depicted.

An excellent bibliography of over 500 references is appended. Some 50 illustrations, largely of surgeons prominent in the development of the specialty, enhance the book.

In a pleasing and easy reading style the book gives an interesting account of the development of the specialty. The subject matter is reasonably complete and accurate; a few errors have crept in, such as the anachronism on page 27, "They (Hippocratic surgeons) advised opening ragged lacerations widely in order to open any pockets which might become the seat of infection," but they detract little from the text. All physicians interested in the development of the specialty will find in this book a clear, concise and authoritative history of neurological surgery.

A. E. W.

Neurology

Occlusion of the Superior Cerebellar Artery

Joseph A. Luhan, M.D. and Seymour L. Pollack, M.D.

ALTHOUGH of rare occurrence, occlusion of the superior cerebellar artery produces so distinctive a clinical picture from involvement of the brachium conjunctivum and long sensory pathways in the upper pontine tegmentum that it has drawn the attention of a number of observers since Mills[1] first described the syndrome in 1908.

Difficulty in its clinical recognition may arise when this occlusion is but one of a series of vascular accidents in the same patient, or if the patient has become confused or weak from the effects of cerebral arteriosclerosis or the influence of grave systemic disease.

Six instances of this syndrome are presented here. The first three cases were clinically obvious, without necropsy confirmation. The fourth patient was only studied pathologically; the focal neurologic symptoms arose in the course of subacute bacterial endocarditis. The fifth patient suffered from the effects of very extensive encephalomalacia in the distribution of one middle cerebral artery, and only by previous findings could one have recognized that the softening in the distribution of the superior cerebellar artery found at necropsy had preceded the more massive cerebral insult. The sixth case was a complicated one, manifested at its onset by initial apoplectiform symptoms simulating those associated with rupture of a basilar intracranial aneurysm. Upon examination some time later there was found, in addition, a syndrome

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typical of occlusion of the superior cerebellar artery. This last case is of special interest as the cerebellum itself was spared, indicating that the lesion in the brain stem alone can account for all of the symptoms.

Case 1.—A 60 year old negro man was admitted to the urology service of the Cook County Hospital on October 28, 1947, because of urinary incontinence, difficulty in voiding and inability to walk. Urinary frequency and nocturia as well as high blood pressure had been present for several years. He had been well otherwise until the evening of October 7, 1947, when he became nauseated and vomited several times. He was able to walk to the bathroom but he required assistance in order to return to his room. Since then he had been aware of weakness of the right arm and awkwardness of the right leg. At no time had he lost consciousness. Nausea and vomiting did not recur after the first night.

Examination: The patient was a chronically ill elderly man. The blood pressure was 170/120. There was moderate emphysema. The heart was enlarged to the left. A soft systolic murmur was present. The urinary bladder was distended.

Neurologic examination showed the patient to be confused and unable to stand unassisted. Severe intention tremor was brought out by the right finger-to-nose and the right heel-to-knee tests. Rapid rhythmic movements were poorly performed with the right hand and forearm. There was a loss of the check reflex in the right limbs. The left limbs showed no evidence of cerebellar dysfunction. There were no paralyses, pareses, atrophies or involuntary movements at rest. A definite impairment of pain and temperature sensation was present over the entire left half of the body, inclusive of the face. Touch, position and vibratory sensations were intact. There was no astereognosis. The deep reflexes were active on the two sides but seemed to be slightly more active on the left. The cremasteric and abdominal reflexes were absent. The Hoffmann sign was present on the left side. There were no pathologic toe reflexes. Olfactory sensation was intact. Visual fields and visual acuity were grossly normal. Fundoscopy revealed mild arteriosclerotic vessel changes. The external ocular movements were full but on the extreme left lateral gaze a nystagmus was noted. The right pupil was smaller than the left. Each pupil reacted to light and in accommodation. A slight narrowing of the right palpebral fissure was noted. A very slight left lower facial weakness appeared when the patient smiled. Taste sensation was intact. The whispered voice was heard at four feet on the right and at one foot on the left. The auditory canals and tympanic membranes were intact. Laryngoscopic examination was normal. There were no swallowing difficulties. There was no palatal paralysis. The other cranial nerve functions were intact.

Cystoscopy showed an atonic bladder with prostatic obstruction. A cystotomy was done on November 1, 1947. The cerebellar dysfunction on the right persisted up to the time of the patient's transfer to another hospital on July 30, 1948. The left-sided hypalgesia had improved somewhat but was still present at that time. The patient was still unable to walk but was up in a wheelchair daily.

Case 2.—A 66 year old negro was admitted to the Cook County Hospital on August 23, 1948, because of inability to walk. He first noticed dizziness while working as a porter, sometime in June 1948. The dizziness lasted through the night and into the next day, when he vomited repeatedly. These symptoms subsided in a day or so and the patient returned to work. He experienced return of dizziness and vomiting while at work on August 18, when he said the room seemed to spin around. This persisted for a few days. Several hours after onset of vertigo the patient vomited repeatedly. He had been unable to walk since recurrence of these symptoms.

Examination disclosed relatively normal physical findings, apart from neurologic disease. His blood pressure was 138/66, pulse 84, respiration 20. The patient was cooperative and his sensorium was clear. Severe intention tremor was seen in the left finger-to-nose and left heel-to-knee tests. Rapid, rhythmic movements were poorly performed with the left arm and the left hand grip was somewhat weakened. There was slight unsteadiness

in the right heel-to-knee test. The check reflex was moderately impaired in the left arm. The patient was unable to stand unassisted. There were no paralyses or atrophies and no involuntary movements at rest. Pain sensation was markedly impaired over the entire right side of the body—trunk, face and limbs. Thermal sensibility was less severely impaired over the entire right side of the body. Touch, position and vibration sensation was well preserved except for inconstant apparent diminution of the position sense of the toes. There was no astereognosis. The deep reflexes were equally active on both sides and no pathologic reflexes were found. The abdominal and cremasteric reflexes could not be elicited. Horner's syndrome was present on the left side, consisting of miosis, narrowed palpebral fissure and diminished sweating over the left half of the face. Fundoscopy revealed mild arteriosclerotic changes. Visual acuity and visual fields were grossly intact. The external ocular movements were normal. There was no nystagmus and the pupils reacted to light and in accommodation. The jaw movements were intact.

The corneal reflexes were present. No definite facial weakness was noted on volitional or emotional innervation. The whispered voice was heard at 11 feet with the right ear and at six feet by the left ear. The Rinne' and Weber tests showed normal results. An audiogram revealed moderate loss of hearing in each ear in the tone ranges from 64 to 1024 vibrations per second, with considerably more deafness in the left ear for higher tones (e. g., 60 per cent loss in the left ear at the 2098 range, compared with 35 per cent loss on the right). Caloric vestibular tests showed some hyporeactivity of the left ear. Laryngoscopy disclosed normal findings. There was no palatal paralysis. Speech and swallowing were intact. All remaining cranial nerve functions were normal.

The cerebellar dysfunction on the left was still present early in October 1948, and had not lessened. The slight unsteadiness in the right heel-to-knee test had disappeared. The patient was up daily in a wheelchair, but was still unable to stand unassisted. Pain sensation of the right half of the body, especially over the face, had returned in a measure, but a definite hypalgesia remained. Temperature sensation had been restored to even greater degree than that for pain, but slight impairment of thermal sensibility was still noticeable.

Case 3.—A 67 year old white man entered the Cook County Hospital on August 19, 1949, because of dizziness and inability to walk. He had felt dizzy on getting out of bed the morning of his hospitalization and fell to the floor. The general physical examination apart from neurologic findings was negative except for the following: right inguinal hernia, apical systolic murmur, liver edge palpable four finger breadths below costal margin, and blood pressure of 148/92.

Neurologic examination revealed a severe intention tremor in the left limbs. The patient could not stand unassisted. The check reflex was moderately impaired in the left upper extremity. No hypotonia could be demonstrated although it was difficult to get the patient to relax completely. There was considerable dysdiadokokinesia of the left upper extremity, aggravated by the intentional tremor. No paralyses, pareses, atrophies or involuntary movements at rest were present. There was a loss of pain sensation over the entire right half of the body—trunk, face and limbs. Temperature sensation was also lost in these areas. Sensation for touch, position and vibration was intact. A left-sided Horner's syndrome consisting of miosis, narrowed palpebral fissure and facial anhidrosis present. The deep and superficial reflexes were active and equal bilaterally. There were no pathologic reflexes. Visual fields and visual acuity were grossly unimpaired. The fundi appared normal. The external ocular movements were normal. There was no nystagmus. The pupils reacted to light and in accommodation. No facial weakness on volitional or emotional expression could be demonstrated. Hearing was somewhat diminished, the whispered voice being heard at six feet with the right ear and at one foot by the left ear. The Weber and Rinne' tests were normal. Caloric vestibular tests revealed normal findings with respect to nystagmus and vertigo. The other cranial nerve functions were intact.

The sensory impairment described above slowly subsided. By October 14, 1949 pain sensation was normal over the face, but was still slightly impaired over the trunk and the

limbs on the right, although the patient recognized pin-prick as touch in these areas. Temperature sensation showed a similar improvement. The severe intention tremor on the left was still present, but the Horner's syndrome had disappeared except for a very slight narrowing of the left palpebral fissure.

Case 4.—A 29 year old Negro man entered Cook County Hospital on March 23, 1946, with complaints of migratory joint pains and sweating episodes of two weeks duration. He had had rheumatic fever at the age of 20 years. Examination showed the apex beat to be in the mid-clavicular line in the sixth intercostal space. There was a mid-diastolic murmur at the apex with a blowing systolic murmur radiating into the axilla. The lung fields were clear. In the hospital the patient's temperature ranged from 99° F. to 102° F., and pulse from 90 to 120. Urinalysis was negative. Hemoglobin was 59 per cent, red blood cells numbered 3,800,000 per cu. mm., white blood cells 17,000 per cu. mm., with 89 per cent polymorphonuclears, 2 per cent lymphocytes and 9 per cent monocytes. Several blood cultures were negative but finally a positive culture for streptococcus viridans was obtained. The patient was treated with 60,000 units of penicillin every three hours and received 35 million units of penicillin over a period of 70 days.

On June 15, 1946, the patient experienced pain in the left eye associated with nausea and vomiting. An intention tremor involving the left arm and leg was noted. The sensations of pain, touch, temperature and vibration were grossly intact, but the patient complained of numbness over the entire right side of the body. Motor power in the left arm and leg was slightly diminished. The deep reflexes on the left side were increased. There were no pathologic toe responses but the Hoffmann sign was obtained on the right side. The abdominal reflexes were absent. The fundi appeared normal. The pupils were normal. The external ocular movements were full but horizontal nystagmus on lateral gaze was present. There was no facial weakness. Speech was slurred. Swallowing was intact. There was no hypoglossal paralysis. The patient left the hospital on September 4, 1946, after being afebrile for approximately 60 days. He was readmitted to the Cook County Hospital on September 19, 1946 in an agitated state with signs of marked cardiac decompensation. He died on September 27, 1946.

Necropsy showed rheumatic pancarditis (recurrent), healed subacute bacterial endocarditis, cardiac hypertrophy, chronic congestion of the lungs, liver, spleen and kidneys and old infarcts in the spleen and kidneys.

The formalin fixed brain showed slight diffuse thickening of the leptomeninges. The terminal part of the basilar artery and the beginning of the posterior cerebrals, especially on the left, and the left superior cerebellar artery presented atherosclerotic changes. Serial coronal sections through the cerebral hemispheres proper revealed no significant abnormalities aside from some postmortem decomposition resulting from poor fixation. The dorsal surface of the left cerebellar hemisphere contained a slightly depressed brownish area about 1 cm. in diameter, evidently the site of a softening. The markedly atherosclerotic left superior cerebellar artery appeared like a thick white string. The terminal 5 mm. of the basilar artery was entirely occluded. The left posterior cerebral artery after its junction with the posterior communicating artery was patent, but showed a 2 mm. beadlike swelling at its origin.

The brain stem presented a 3x7 mm. softening in the tegmentum of the rostral pons, just beneath the locus coerulus on the left side. Myelin stained sections through the rostral pons containing the area of gross softening showed a small area of necrosis just above the medial lemniscus on the left, destroying the ventral portion of the brachium conjunctivum on that side (figure 1). The median longitudinal fasciculus on the left was practically demyelinized. The cerebellar folia adjacent to this area of necrosis were completely demyelinized and shriveled. This area of destruction in the pontine tegmentum was in the nature of an organizing anemic softening. Remnants of the softening were seen as far caudally as the level of entrance of the fifth nerve.

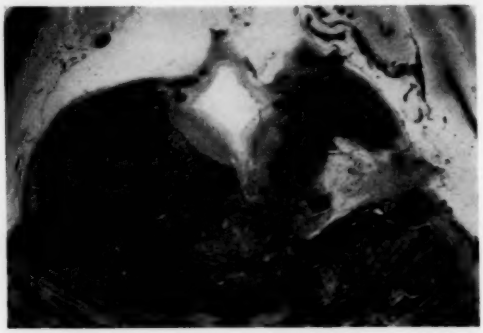

FIG. 1. Section through the rostral pontine (ponto-mesencephalic) tegmentum at the level of the trochlear nerve, showing destruction by encephalomalacia of the inferior part of the left brachium conjunctivum and partial demyelination of the left median longitudinal fasciculus. Pal-Kultschitzky stain.

This was a case of occlusion of the terminal portion of the basilar artery, the beginning of the left posterior cerebral artery and the entire left superior cerebellar artery by an infected embolus, with destruction by anemic softening of the ventral third of the left brachium conjunctivum, partial demyelinization of the left median longitudinal fasciculus, very slight involvement of the lateral portion of the medial lemnicus, and softening of some of the adjacent cerebellar folia maximally developed at a rostral pontine level.

Case 5.—A 38 year old negro woman was admitted to the gynecology service of the Cook County Hospital on July 8, 1948, for the treatment of fibroid uterus. On July 13, 1948, a supracervical hysterectomy and bilateral salpingo-oophorectomy was performed. Postoperatively her temperature was elevated to 100° F. but she had no difficulties until July 18, 1948, when she complained of severe pains in both calves, which were slightly tender. On July 20 she began complaining of "numbness and loss of life" in her left side.

Neurologic examination on July 28 disclosed an absence of pain sensation over the entire left side of the body, including the face. Touch sensation was somewhat impaired in the same area. The right finger-to-nose test revealed slight intention tremor. Some incoordination was shown in the right heel-to-knee test. No motor weakness was present and there were no involuntary movements at rest. The right pupil was somewhat constricted. Both pupils reacted to light and in accommodation. The right palpebral fissure was narrowed. Visual acuity and visual fields were grossly intact. The fundi appeared normal. The external ocular movements were of full range. No nystagmus was present. The muscles of mastication were intact. The corneal reflexes were present. There seemed to be some left lower facial weakness on emotional expression. Hearing was grossly intact. Swallowing and speech were intact. There was no palatal paralysis. The biceps, triceps, radioperiosteal, patellar and Achilles reflexes were active and equal bilaterally. Bilateral Hoffmann finger signs and Babinski signs were present. The abdominal skin reflexes were present.

On the evening of July 23, 1948, a few hours after the foregoing examination was made, the patient suddenly became stuporous, and hemiplegic on the right side. On July 26, the red blood cell count was 2.70 million per cu. mm., the hemoglobin 50 per cent, and the white blood cell count 12,400 per cu. mm. On July 30, the patient seemed to be more alert but still could not speak. She remained lethargic and continued to show an elevated temperature indicative of a septic course. Blood transfusions were given to little avail. Tube feedings became necessary. A blood culture taken on September 25, 1948 showed nonhemolytic staphylococcus aureus. The septic course of her illness was unchecked by antibiotic treatment and she expired on October 19, 1948.

The general autopsy examination revealed old verrucous vegetations of the mitral valve, dilatation of all cardiac chambers, pulmonary edema, parenchymatous degeneration of the

kidneys, acute ascending pyelonephritis, acute splenitis and fatty metamorphosis of the liver.

Examination of the formalin fixed brain disclosed extensive anemic encephalomalacia in the left cerebral hemisphere in the distribution of the left middle cerebral artery (figure 2) and an area of encephalomalacia involving the right rostral pontine and junctional caudal mesencephalic tegmentum and adjacent cerebellum, in the distribution of the right superior cerebellar artery. Each of these infarcts was probably of embolic origin. At the cross sectional level of the fourth nerve and pontomesencephalic junction there was extensive softening with irregular cavitation in an area 5x15 mm. in cross sectional dimensions, in the tegmentum on the right side, destroying the brachium conjunctivum. The caudal part of the cerebral aqueduct and the beginning of the fourth ventricle were enlarged. The caudal limit of the pontine softening was 3 mm. rostrad to the point of entrance of the fifth nerve. There was an extensive, yet superficial dirty brownish colored softening on the dorsal surface of the right cerebellar hemisphere. There was no gross softening in the right dentate nucleus. The superior cerebellar artery so far as it could be observed without dissection appeared patent. Microscopic sections revealed incomplete softening in the dentate nucleus. A section through the caudal midbrain near the rostral limit of the softening stained for myelin is shown in figure 3. Sections through the medulla oblongata stained by the Weil method revealed slight hypertrophic degenerative change in the left inferior olive and conspicuous pallor of the left thalamo-olivary tract.

Case 6.—A 36 year old woman who had borne six children previously was seven months pregnant when admitted to the obstetrical service of Cook County Hospital on July 1, 1950. She had had a sudden onset earlier that day of headache, vomiting and loss of consciousness, followed by weakness of the left extremities and double vision. Apparently she had suffered from a transient apoplectiform cerebral episode manifested by delirium about six years previously, from which she had recovered in a week. On admission the patient was drowsy and uncooperative but she was found to have hemiparesis on the left without pathologic reflexes, marked dysarthria, downward and inward deviation of the right eye, and constricted pupils. Her blood pressure on admission was 126/76, temperature 98.8° F., pulse 76, respirations 30. Next day the hemiplegia was said to have disappeared with persistence of right lateral rectus weakness and presence of right-sided ptosis. Spinal puncture on July 3, 1950 revealed a grossly bloody fluid with a colorless supernatant liquid after centrifugalization. The initial spinal fluid pressure in the lateral recumbent position was 190 mm. of water; the total protein content of the fluid was 56 mgm./100 cc. and the Wassermann reaction on 0.5 cc. of fluid was negative. Blood drawn on the same day yielded a negative Wassermann reaction.

Neurologic examination on July 6 disclosed: marked lethargy; inability to stand; dilatation of the right pupil, internal strabismus of right eye from weakness of the lateral rectus; left sided hemiparesis including the lower face; deviation of the tongue toward the left on protrusion; Hoffmann sign, absent abdominal reflexes, and Babinski sign on the left side; nystagmus on left lateral gaze; dyssynergy (decomposition of movement) in left upper extremity during the finger-to-finger and finger-to-nose tests; sensation could not be reliably tested. A second spinal puncture on July 18 revealed clear, colorless fluid containing 26 mgm. of protein per 100 cc.; the pressure was not measured.

On July 18, 1950, she was found to be confused, euphoric, restless and irritable, and was believed to be experiencing visual hallucinations. Her attention wandered and cooperation was poor. The right pupil was distinctly smaller than the left and the palpebral fissure of this eye was narrowed. There was weakness in abduction and elevation of the right eye during conjugate movements. Mimetic lower facial paresis on the left and deviation of the tongue to this side on protrusion was noted. There was marked ataxia with wide swaying aggravated by intentional effort during movements of the right upper extremity, as in the finger-to-nose test; in the left hand slight apparent ataxia without swaying or tremor was observed, and it was thought there was slight motor weakness here. Some dysmetria

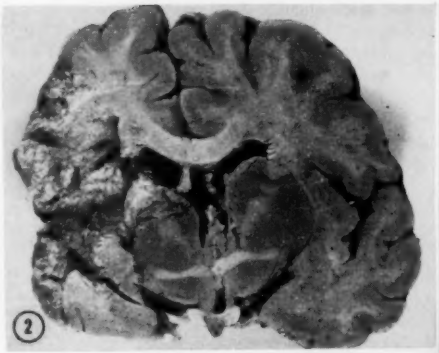

FIG. 2. Extensive anemic encephalomalacia in the distribution of the left middle cerebral artery.

FIG. 3. Section through the caudal midbrain showing softening in the tegmentum on the right side. Pal-Kultschitzky stain.

in the heel-to-knee tests was noted on both sides. There was marked left sided hemihypalgesia (inclusive of the face) to pinprick, while gross touch, joint sense and vibratory sensation were apparently not significantly altered. The left abdominal reflexes were absent, those on the right side diminished, while the deep tendon reflexes and plantar responses were normal.

The patient continued to be somewhat confused, emotionally unstable, restless and at times quite disoriented during the next week, and then became calmer and better oriented. There were no further visual hallucinations. A vertebral arteriogram was performed on August 10 and was normal. As soon as the patient awakened from the effects of the anesthetic (sodium Pentothal), she went into labor, and while being transferred to the obstetrical ward, experienced a generalized convulsive seizure. She began to vomit and on two occasions aspirated vomitus, which later became bloody. She died about 24 hours after performance of the arteriogram.

Necropsy revealed pulmonary congestion and edema, fatty change of the liver, and a vascular lesion of upper brain stem on the right side. There was some flattening of the surface cerebral convolutions and a slight degree of herniation of the cerebellar tonsils. The large vessels at the base were thin walled and patent, and no aneurysmal formations were seen. The right superior cerebellar artery was seen to divide into two branches about 4 mm. from its origin, and the larger of these, almost a millimeter in diameter, was filled with a soft clot. When the brain stem and cerebellum were severed from the rest of the brain through the midbrain, a diagonally coursing linear friable brownish softening was seen in the tegmentum of the caudal mesencephalon, while the cerebellar cortex appeared intact. This lesion could be followed through the rostral pons, where practically the whole of the right brachium conjunctivum had undergone encephalomalacic destruction, while the cerebellar structure was well preserved (figure 4). In a cross sectional slice just rostral to the point of entrance of the fifth nerves the lesion had the form of a brownish hemorrhagic softening of the brachium conjunctivum, bulging tumor-like for a few millimeters in to the lumen of the fourth ventricle on the right side (figure 5). Further sectioning of the brain

stem disclosed a hemorrhage in the right superior colliculus continuous with a linear softening in the tegmentum of the midbrain (figure 6). A nearly horizontal section through the midbrain revealed a diagonal cleft in the tegmentum from 1 to 3 mm. wide, 10 mm. long, extending from above the substantia nigra to near the cerebral aqueduct. In Nissl preparations it had the typical appearance of a cavity resulting from hemorrhagic softening, still containing numerous gitter cells, many laden with hemosiderin pigment. The margins of the softening were the site of gemistocytic glial reaction. The softening reached superomedially to involve a few cells of the third nerve nucleus. There were small hemorrhages about thrombosed small vessels in the superior colliculus. Sections through the right dentate nucleus revealed ischemic ganglion cell disease and diffuse polymorphonuclear infiltration, as in beginning softening. The medulla oblongata showed hypertrophic degeneration of the left inferior olivary nucleus (figure 7).

Sections of the remainder of the brain, particularly from the frontal convexities, revealed hyperemia and edema of the surface leptomeninges, which contained proliferated arachnoidal cells, some mononuclear cells and histocytes bearing hemosiderin pigment. The first cortical layer showed fairly conspicuous deposits of hemosiderin granules. Some of the larger cortical ganglion cells presented the staining appearance of so-called acute ganglion cell disease.

The presence of these hemosiderin granules in the meninges and first cerebral cortical layer suggested that the patient had suffered from subarachnoid bleeding some weeks or months previously.

The distribution of the softening, which may well have been embolic in the absence of demonstrable occlusion by old or organized clot in the free portions of the superior cerebellar artery, was quite typical for this artery in the pons, but unusual with respect to the midbrain at the level of the superior colliculus. The blood supply of the superior colliculus comes from an arterial plexus supplied mainly by the artery to the quadrigeminal tubercles derived from the posterior cerebral artery, but this anastomoses with branches of the superior cerebellar artery, which ordinarily supplies the inferior colliculus (Alezais and d'Astros[2]). It could not be determined by inspection whether the midbrain lesion involving in part the superior colliculus was a result of involvement of the superior cerebellar artery or of a branch of the posterior cerebral artery, since the plexus of vessels in the vicinity of the superior colliculus was free from thrombi, but it was presumed that the lesion was within the distribution of the posterior cerebral artery.

COMMENT

A number of the reported cases of occlusion of the superior cerebellar artery verified by necropsy have been poorly studied from a clinical standpoint, and other vascular lesions (apart from encephalomalacia in the one superior cerebellar artery distribution) have been found in nearly every case. In the largest series reported only four of the nine cases had any validity with respect to correlation of disturbance of function with site of lesion.[3] The case described by Guillain, Bertrand and Péron[4] closely resembled that of Mills.[1] Critchley and Schuster's excellent study was concerned with six cases, but only three are admissible as relatively uncomplicated cases from which valid clinicopathologic inferences might be drawn.[5] Thompson's report of five cases of embolic occlusion of the superior cerebellar artery is a pathologic study, with clinical evidence of the characteristic syndrome either minimal or overlooked.[6] However, Thompson indicates how this artery is more susceptible to embolic blocking than are the anterior inferior and posterior inferior cerebellar arteries.

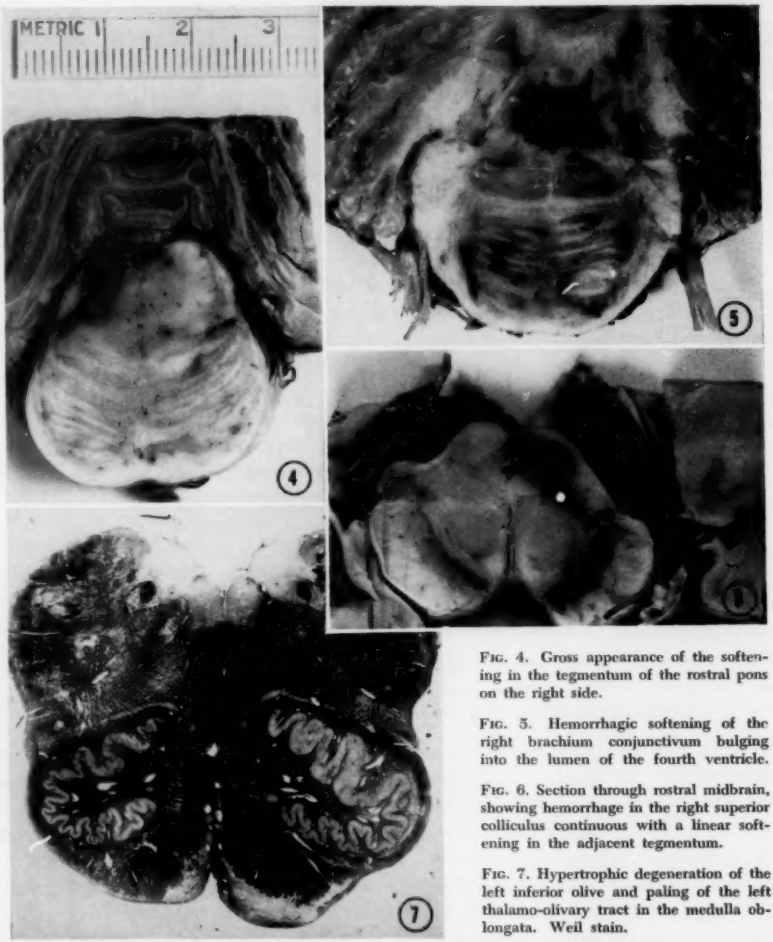

FIG. 4. Gross appearance of the softening in the tegmentum of the rostral pons on the right side.

FIG. 5. Hemorrhagic softening of the right brachium conjunctivum bulging into the lumen of the fourth ventricle.

FIG. 6. Section through rostral midbrain, showing hemorrhage in the right superior colliculus continuous with a linear softening in the adjacent tegmentum.

FIG. 7. Hypertrophic degeneration of the left inferior olive and paling of the left thalamo-olivary tract in the medulla oblongata. Weil stain.

The revealing clinicopathologic single case study by Russell[7] called attention to the syndrome after it had been largely overlooked in the literature since Mills' report of the clinical syndrome in 1908. It is interesting that here too another vascular lesion had complicated the clinical picture. Freeman and Jaffe[8] in 1941 reviewed the literature and reported one case of a man who died two months after embolic occlusion of the superior cerebellar artery, and studied the resulting secondary degeneration by the Marchi method. As in

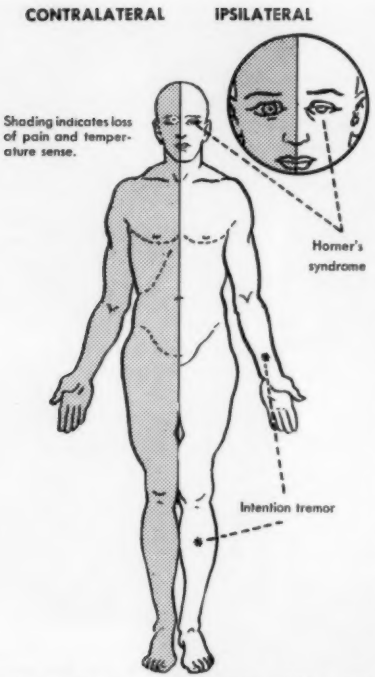

FIG. 8. The syndrome of occlusion of the superior cerebellar artery.

the case of previous investigator found hypertrophic degenerati the inferior olivary nucleus o lateral to the cerebellar softeni

The fully developed syndro occlusion of the superior cer artery includes ipsilateral cer dysfunction, loss of pain and te ture sensation or subjective nu in the total contralateral distri ipsilateral Horner's syndrome variable findings of hearing lo of impairment of mimetic fac nervation on the opposite sid ure 8). These components of th drome will be discussed briefly separate headings.

1. *The cerebellar dysfun* This occurs ipsilateral to the sion and is due to involvem the brachium conjunctivum a nucleus of origin, the dentate n Both of these structures are su by the superior cerebellar arter dentate nucleus sends fibers brachium conjunctivum to the site red nucleus and to the o ventrolateral nucleus of the tha the latter in turn projects to the motor and premotor cortex. This d thalamic pathway is the main projection of the dentate nucleus in m is a neocerebellar projection producing a neocerebellar syndrome w terrupted.[9] To produce this ipsilateral cerebellar disturbance the bra conjunctivum must be interrupted before its decussation. The soften sulting from occlusion of the superior cerebellar artery involves the bra conjunctivum. The tremor in our cases of this syndrome appeared duri untary movement and is best described as an intention tremor. The bas turbance in this syndrome is one of voluntary movement which is a n bellar disturbance. Bailey[10] has recently discussed the functions of th cerebellum. The cerebellar dysfunction in cases of occlusion of the su cerebellar artery results from the lesion in the brain stem and not fro softening in the cerebellar cortex, as is attested by our case 6, and ca Davison et al.,[3] each with the cerebellar cortex practically intact.

It is of interest that mention of intention tremor, a characteristic in all our cases, was sometimes lacking in earlier reports. Mills[1] state his patient had marked ataxia, almost amounting to intention tremor,

upper extremity, with no ataxia in the heel-to-knee test. The upper extremity may be more affected than the lower, as was noticed in our case 6. Russel[7] did not mention intention tremor in his case but stated that the ataxia of the arm and leg was especially marked toward completion of the act of touching the nose and in the heel-to-knee test. Only in case 2 of Davison et al.[3] was there specific mention of intention tremor, although Critchley and Schuster[5] found this (if "Wackelzittern" can be so translated) in all of their five cases in which some clinical examination had been possible.

2. *The loss of pain and temperature sensation.* In the fully developed syndrome of occlusion of the superior cerebellar artery, pain and temperature sensation are lost in the entire half of the body contralateral to the occlusion. A lesion in the rostral pons or caudal midbrain within the distribution of the superior cerebellar artery will produce this contralateral sensory loss by interrupting the spinothalamic tract and the secondary trigeminal pathways for pain and temperature. The spinothalamic and secondary trigeminal pathways have been described by Walker[11] in a series of articles. He states that at the rostral margin of the brachium pontis the fibers of the spinothalamic and secondary trigeminal pathways reach the periphery of the brain stem near the lateral sulcus. In the mesencephalon these tracts lie among the fibers of the lateral and not the medial lemniscus.

Because of vagaries of anatomic distribution and collateral circulation with respect to the superior cerebellar artery, the spinothalamic and quintothalamic tracts may be only mildly damaged, resulting in numbness, as in our case 5. Although without necropsy control Girard, Bonamour, Garde and Etienne[12] described paresthesia and spontaneous pain in the contralateral sensory distribution in one case, otherwise atypical because moderate hemiballismus preceded development of the cerebellar hemisyndrome.

3. *The Horner's syndrome.* This is not invariably present. It would probably be more accurate to say that this aspect of the syndrome is often not mentioned in the case reports. Freeman and Jaffe,[8] who noted the presence of this finding in their case, remarked that it had not been previously observed, although Critchley and Schuster's[5] case 5 was marked by an ipsilateral Horner's syndrome, and occasionally other writers noted slight ipsilateral narrowing of the palpebral fissure. This finding was present in five of our six cases. An ipsilateral Horner's syndrome occurs in other brain stem lesions, as after occlusion of the posterior inferior cerebellar artery.

4. *The hearing impairment.* Occasionally this occurs contralateral to the occlusion. The lateral lemniscus lies in close proximity to the pain pathways in the rostral pons and may be damaged. The lateral lemniscus is mainly a crossed tract but many of its fibers arise from the cochlear nuclei of the same side. Individual variations undoubtedly exist. This bilateral projection from the cochlear nuclei would tend to mask any hearing impairment resulting from slight damage to the lateral lemniscus.

5. *The loss of emotional expression on the analgesic side.* We were unable to demonstrate the loss to our complete satisfaction except in one or two cases. It has been reported as obvious in some of the cases in the literature, while in other cases no mention is made of it. The pathways for emotional expression are not clearly understood, and to discuss them would take us too far afield. However, it is known that such a disturbance may occur in thalamic or high brain-stem lesions.

6. *Miscellaneous findings.* Our cases did not show the ipsilateral involuntary movements at rest, mentioned by other observers.[3,4,12] It is difficult to give an adequate explanation for these movements. Neocerebellar pathways are mainly implicated in occlusion of the superior cerebellar artery and these pathways influence voluntary, not involuntary movements.

Sixth nerve paresis has occasionally been observed (as in cases 6 and 7 of Davison et al.[3]) probably dependent on an unusual distribution of the artery, with extension of softening to implicate the sixth nerve or nucleus. The initial abducens weakness in our case 6 was not explained. This same patient showed transient, partial third nerve weakness explainable on the basis of edema because of the complicating midbrain lesion. One wonders why some weakness of the fourth cranial nerve has not been found in some of these cases, as was reported by Girard et al.[12] in two cases, each of them atypical and one without necropsy control. The fourth nerve weakness occurred on the side opposite the lesion (opposite to the cerebellar symptoms) as might be expected from a nuclear involvement of this crossed nerve. Incidentally, the second patient of these observers presented a rhythmic myoclonus of the palate, pharynx and larynx.

Nystagmus has been noted now and then by previous writers (as in case 6 of Davison et al.[3]). The nystagmus noted in our case 4 was correlated with implication in the lesion of the median longitudinal fasciculus.

SUMMARY

Six cases of unilateral occlusion of the superior cerebellar artery, three with necropsy control, are presented. This condition is characterized by a distinctive clinical syndrome: sudden onset without loss of consciousness, marked usually by vomiting, often by dizziness, and by inability to stand or walk; ipsilateral cerebellar dysfunction, particularly tremor of intention, and usually Horner's syndrome on the side of the lesion; loss of pain and temperature sense or subjective numbness in the total contralateral distribution; sometimes contralateral impairment of mimetic facial innervation; and inconstant occurrence of nystagmus and hearing loss, not clinically reliable as indices of lateralization.

These symptoms arise because of interruption of the brachium conjunctivum, the lateral spinothalamic and quintothalamic pathways, descending oculosympathetic fibers, and sometimes the lateral lemniscus and median longitudinal fasciculus in the tegmentum of the rostral pons.

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The cerebral diseases affect primarily the cerebral functions, and the true spinal functions consecutively. The diseases of the true spinal system induce changes in the excito-motory phenomena, in the first place, and in the cerebral functions in the second. The cerebral diseases are generally more insidious in their progress than the true spinal, because slight aberrations of the cerebral functions are less observable than similar affections of the true spinal: pain, vertigo, watchfulness, &c. are less striking than the slightest degree of convulsive movement, or paralytic affection. It is on this account that the *first* symptom *observed* in cerebral disease, is frequently one belonging to the true spinal system, especially *vomiting*, perhaps *strabismus*.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Studies on the Cervical Spinal Cord of Man

Sensory Pattern after Interruption of the Posterior Columns

Benjamin Boshes, M.D. and Frank Padberg, M.D.

WHEN a patient experiences the loss of ability to recognize by palpation the form and nature of an object, that defect is usually called "astereognosis." Assuming that the palpating part has relative integrity of motor power and preservation of the modalities of touch, temperature and pain, the disability is usually ascribed to a lesion of the contralateral parietal lobe. This thinking has resulted in many mistaken diagnoses, often in cases amenable to surgical intervention.

The great upsurge in neurologic surgery since World War I and the frequency of tumors in the parietal lobe led diagnosticians to seek early critical signs. Among these was astereognosis. Errors in localization soon followed and were documented in the literature, but the term persisted in the textbooks even though it was used in situations for which it was never intended. In 1923, after one such error, Cushing stated,[1] "Mr. E. H.'s astereognosis made us suspect a parietal lobe lesion. We . . . shall hereafter regard astereognosis as a symptom which may accompany a tumor in the posterior portion of the cerebellum, which can in some way involve the sensory pathway." Even Foster Kennedy[2] used the term in describing a defect arising from lesions in the cortex, subcortex, thalamus, spinal cord and peripheral nerve.[2] Others reported similar instances leading to faulty localization.[3–6] More recently Rubenstein brought up to date the literature on this pitfall in diagnosis when the

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f function is not clearly defined. However, he too persisted in using the astereognosis."[7] He reviewed the evolution of the word "stereognosis," uced in 1885 by Hoffman to denote "a recognition through palpation of rm of an object in its three dimensions."

e interruption of neural activity in the aforementioned cases did not at a cortical or gnostic level where there are elements for associative ther psychic phenomena, such as reproduction of memory pictures. The erence took place at a site where the sensory pathways were converging he medulla on their way up to the thalamus. Hence the defect is not sis but in conduction of the modalities which subserve space perception. s stereoanesthesia, a term which we encountered first in the 1915 edition g.[8] In his lecture on tabes dorsalis, Bing described "disturbance of posi- nd movement sense in fingers" as "stereoanesthesia." Schott,[9] Tilney iley,[10] Brock[11] and DeJong[12] all use the term and point out, "One can- iagnose this (astereognosis) if peripheral sensations are diminished or ."[12] Schott tabulated the sensory defects in the hand in his cortical and rtical cases and concluded that he was unable to differentiate between o types of loss. Rubenstein[7] points out that in the presence of "astere- s" the following findings are of value in placing the lesion in the region foramen magnum: "Rheumatic" pains about neck and shoulders, stiff- f the neck, a tendency to restrict the motion of the head or to keep it to one side in a forced attitude.

h suggestions are helpful, and others have tried to describe further aids p differentiate parietal cortex from other locations when deep sensibility was the presenting symptom. Thus Weinstein and Bender[13] noted that deep sensibility dissociation was found in tumors of a cerebral hemi- , position sense was either lost or markedly impaired while vibration ption was spared or little affected. At the brain stem or upper cervical position sense was markedly impaired while vibration was affected to bly lesser degree. At the lumbar or thoracic level, however, vibration ffected earlier and more severely in the lower limbs. The sensibilities rned with spatial relationship have a large cortical representation. When n sense is lost, astereognosis and faulty two-point discrimination occur. ntrast, vibration sense, not concerned with space, does not suffer much cortical lesions.

our studies we employed the usual tests for deep and superficial sensa- In addition to testing the affected limb for object recognition we also d the numeral or figure-writing test. This was originally devised by ler[14] to localize a lesion in the posterior columns when other level signs lacking. Few textbooks mention the test except Cadwalader,[15] Monrad- [16] and Wechsler[17] who like Cadwalader calls it "graphesthesia." Warten- renewed interest in numeral writing in 1939 when he pointed out its ite ability to detect the level of a spinal cord lesion affecting the pos- columns. While most investigators employ this test for spinal cord

TABLE I

Loss of pain sense	*Loss of temperature sense*	*Loss of cotton touch sense*	*Ataxia*	*Loss of position sense*	*Loss of vibration sense*	*Loss of object-in-space sense*	*Loss of "numeral writing" recognition*	*Other signs*
Case 1. Female Age 26. Ependymoma at Foramen Magnum and Upper Cervical Cord								
C.2-T.4 on left	Mild left arm	Mild C.2-T.9 on right	Right arm severe	Right arm severe	Right arm severe	Severe	None	Bilateral papilledema. Pyramidal tract signs on right.
Case 2. Male Age 22. Hemangioblastoma at Lower Medulla. C.1-2								
Mild, left arm, left face	Left arm and hand	Left C.2-3, Right C.4-7	Both arms, greater on left	Left arm moderate. Right arm severe	Both arms	Both hands	None	Bilateral papilledema. Truncal ataxia.
Case 3. Male Age 45. Astrocytoma C.1-2-3 Lower Medulla—Chiefly Left but Across Midline								
Mild, left half of body	Mild, left half of body	Mild, left half of body	Left arm	Left forearm and hand	Left half of body	Left hand severe. Right hand mild		Nystagmus on looking to left or right. Local weakness and reflex changes.
Case 4. Male Age 49. Hemangioblastoma—Midline at Level of Vermis and Upper Cervical Cord								
Mild, left arm and face	Mild left arm	None	Bilateral greater on left	Bilateral greater on left	Severe on left	Severe left	None	Bilateral papilledema. Local weakness. Reflex changes.
Case 5. Male Age 44. Syringomyelia C.1-7								
C.1-5 and face on right. Mild C.1-5 and face on left	Mild C.4-5 on right	Mild C.1-5 face—both sides	Both arms greater right	Both arms severe	Both hands severe	Both hands severe	None	Local muscle and reflex changes.
Case 6. Female Age 43. Meningeoma at C.3.								
C.4 down on left	C.7 down on left, mild to C.4	L.5 down on left. T.4-12 on right	Both arms and legs, greater on left	Bilateral, arms and hands	Moderate in left Right upper and lower extremities		Not tested	Local weakness and clumsiness, tingling at level.
Case 7. Male Age 36. Neurofibroma C.2 Left								
Mild left hand	Mild left hand	Minimal loss left little finger	Severe left hand and arm	Left arm and hand	Fingers of left hand	Severe left hand	None	Local atrophy left hand, weakness.
Case 8. Female Age 33. Ependymoma. Lower Medulla to C.3								
Both upper extremities	Both upper extremities	Both upper extremities	Bilateral, greater on right	Both upper extremities	Both upper extremities	Both upper extremities	Not tested	Atrophy and reflex changes at level of lesion.
Case 9. Female Age 59. Metastasis from Breast Carcinoma to Left Thalamus								
Severe right side	Severe right side	Severe right side	Severe right side	Severe right side	Moderate right side	Complete	Severe right side	Burning of pain right half body. Pathological reflexes on right.
Case 10. Male Age 25. Embryonal Cell Carcinoma of Right Testicle with Metastasis to Right Parietal Cortex								
None	None	None	Some on finger-to-nose on left	None	None	None	Severe right lower limb from buttocks down	Sense of numbness left leg. Mild weakness left lower limb. Jacksonian seizures on left.

localization, both Wechsler[17] and Temple Fay[19] consider it essentially a cortical sensory sign. The latter speaks of it as a gnostic sense including two-point discrimination as well as visual projection into numerical concepts. It requires the posterior columns, parietal lobe, visual speech and motor speech centers for the elaboration. Figures are much simpler to test than two-point discrimination.

Our material consisted of eight anatomically verified cases of cervical cord lesions, seven tumors, and one syringomyelia, in all of whom there was a disturbance in one or more phases of deep sensibility or its recognition. In contrast, one case of thalamic tumor and one verified parietal lobe tumor are presented.

CASE HISTORIES

Case 1.—A 26 year old woman with onset of an intermittent dull aching pain in back of neck associated with frequent episodes of nausea and vomiting six years previously. Weakness and a wooden sensation in the right upper extremity gradually increased. Three years after onset she developed attacks of sinking feeling associated with periods of deafness and blindness and some throbbing in left eye. In fourth year after onset she had head pains chiefly in the occipital area, radiating over the vertex of frontal area. One month before admission she complained of intermittent diplopia and nocturia. There had been a weight loss of 20 pounds in the past year. She had had a mastoidectomy at age seven, followed by right facial paralysis.

Examination: Large superficial scar over the mastoid. Frequent vomiting during examination. Head tilted with chin pointing to left; when passively turned she complained of generalized pain in the neck and weakness. Palpebral veins full, especially on left. Bilateral papilledema. Pupils large, equal and reacted normally. Extraocular muscle movements normal. Right facial weakness. Strong itching sensation on right side of face.

Right upper extremity spastic with tendency to fall away. Marked awkwardness, past-pointing and dysmetria of right upper extremity. Many associated movements on right. No ataxia on heel-to-knee test, but left leg stronger than right. Neck resistant to flexion. All deep tendon reflexes brisk, more on right. Abdominal reflexes present, more active on right. Corneal reflexes normal. Bilateral Babinski sign present as well as a right Hoffmann sign. Bilateral ankle clonus and right patellar clonus. Check reflexes preserved. Decreased perception to pinprick over left arm and upper check, T2–T4. Perception to cotton touch diminished from C2–T9 on right. Vibration sensation normal below anterior superior spine on left, but decreased on right; markedly diminished from lower ribs upward, with loss greater on right than on left. Vibration sense completely absent in the right upper extremity. Joint sense present in the lower extremities and in left hand; completely lost on the right hand. Heat and cold less well perceived on left arm than right. Able to recognize skin writing on both palms and forearm.

At operation, a yellow-greenish tumor found on the upper cervical cord. It extended up under the cerebellum into the right cerebellar hemisphere and over the medulla. The tumor was classified as an ependymoma. Four and a half years later this woman is still alive, and is able to walk and get around.

Case 2.—A 22 year old man who complained of subjective numbness in left hand of four years' duration. The left hand would not "obey," and he was unable to play baseball. Occipital headaches had been present for one year, finally associated with nausea and vomiting. He began to drop objects placed in right hand without knowing he had dropped them. There was progressive clumsiness of the right hand with numbness in the right thumb and index finger, and gradual inability to walk to right. He had also noticed

transient left facial weakness, diplopia, progressive instability of gait of left lower extremity, and occasional black-out spells with feeling of spinning around objects. The black-outs came on with change of position.

Examination: Truncal ataxia. Walked with wide staggering gait. Bilateral severe papilledema. Constriction of visual fields; dilated pupils. Left nasolabial fold flat with wide left palpebral fissure. Postural deviation to right on Babinski-Weil test. With patient in supine position and arms outstretched, left arm drifted backward and to right. Drift increased with eyes closed. Past-pointing with the right arm with much decomposition of movement, dysmetria and ataxia in both arms. Left upper extremity extremely difficult to manipulate when patient's eyes were closed because he would "lose it." Marked ataxia with overshooting on heel-to-knee test, greater on left. Deep reflexes brisk, greater on left. Abdominal reflexes absent. No pathologic reflexes in lower extremity. Hoffmann sign on right. Loss of Gordon Holmes-check reflex in the right upper extremity, less so on left. Hypalgesia over the index and middle fingers of left hand extending along the radial aspects of the forearm and arm onto chest and axilla. Loss of pain and touch C4–C7 on right, and C2–C3 on left. Response of left face to pinprick and touch less than on right. Vibration sense diminished over lower extremity, entirely absent over both upper extremities. Position sense present over both great toes. Complete loss of sense of movement of fingers of either hand. Object placed in hand promptly dropped and patient groped for it in mid-air, even though object had been dropped. Finger writing on palm of both hands and forearms promptly recognized.

At operation a large mass was found at the junction of the spinal cord and medulla, 5 cm. long and 2.5 cm. wide. This proved to be a hemiangioblastoma. Patient is alive four years later although he experiences some difficulty in walking and some impairment of vision.

Case 3.—A 45 year old man gave a history of numbness of the ulnar side of the left forearm for one year which spread to involve entire upper extremity, accompanied by clumsiness and inability to hold objects in the hand. Four months after onset, the numbness spread to the left foot and then to the remainder of left lower extremity. He gradually developed left-side occipital-parietal headaches associated with pain over the cervical spine. Weakness of left lower extremity set in, together with difficulty in swallowing solid food. He had poor use of left hand, progressive numbness of the left body, and "astereognosis" in left hand.

Examination: Oscillatory nystagmus on looking to left and right. Right palpebral fissure smaller than left. Weakness in left hand grasp. Falling away of the left outstretched upper extremity. Finger-to-nose test on left poorly done. Left arm less resistant to passive flexion. Poor performance of alternating movements on left. Inability to approximate left thumb to index finger. Dysmetria and loss of coordination of left upper extremity. No mirror writing. No agnosia. No important reflex changes. No pathologic reflexes. Left hemihypalgesia and hypesthesia. Vibratory sense lost over left foot and tibia, also lost below left elbow and diminished over left clavicle and left upper chest. Joint position sense lost in fingers of left hand. Good appreciation of skin writing but inability to recognize objects placed in right hand. Pneumoencephalograms revealed dilatation of all ventricles. Electroencephalogram normal. Radioactive di-iodo-fluorescin test showed persistent concentration of dye in right posterior fossa and upper spinal cord.

At operation, a tumor was found under the foramen magnum on the left side extending across the midline where it came out from beneath the vermis of the cerebellum. This was a mixed astrocytoma.

Case 4.—A man, aged 49, had had bilateral frontal headaches one year, with personality change and loss of interest in previous neat habits. The headaches were associated with changes in position of head and neck. Hyperextension of neck produced pain radiating from neck to vertex. Movement at times was associated with nausea and vomiting. Dim-

vision and some blurring when reading were noted. During the month before ad- to hospital he was reportedly confused at times, had a very poor memory for recent and occasionally had difficulty enunciating words. He also veered to right when and was unable to walk a straight line. He had marked difficulty in picking up A spinal puncture at this time was followed by a severe bout of nausea and vom- The patient had always had a weakness of left lower extremity since age of six when stepped on his left foot, fracturing it. A fall from a horse while playing polo 11 fore had resulted in a neck injury.

mination: Spoke with a halting speech without slurring or stammering. Head held chin pointing to left. Walked with unsteady gait and a slight limp. Undressed difficulty using left hand clumsily; numerous associated movements of this extrem- lateral papilledema with small flame-shaped hemorrhages and engorged retinal veins. fields showed moderate enlargement of blind spots. No nystagmus. Extraocular r movements well done. Widened palpebral fissure on left and left side of face did e as well as right. Left hand grasp much weaker than right with general weakness xtremities, more marked in upper. Slight falling away of outstretched upper extrem- xtended arms, with patient lying, very tremulous with tendency to drift outward as he closed eyes. Slight ataxia on the finger-to-nose test, greater on left and very t dysmetria, more marked on left. Past-pointing and considerable adiodokokinesia, arked on left. Slight ataxia on heel-to-knee test, greater on left. Atrophy of entire er extremity, maximal in the tibialis anticus and extensor group of muscles, with weakness in eversion of foot and tendency toward hammertoe.

ht triceps and biceps reflex markedly decreased. Right wrist and ulnar jerks less han left. Left knee jerk much more active than the right and crossed adduction ion seen when right knee is tapped. Achilles reflexes depressed, the left more active ght. Nonsustained ankle clonus on right with moderately sustained clonus on left. nal reflexes present but left diminished; same true for cremasteric reflexes. Babinski left; none on right; left Hoffmann sign. Pinprick more accurately felt over right face and right upper extremity than on left. Vibratory sensation present throughout critical on left than right. Objects placed in left hand handled clumsily with failure gnize shape and size. Able to recognize numbers written on the left arm. Cotton ormal throughout.

by evidence of old injury at the bodies of the 5–6–7 cervical vertebrae. Ventricu- y revealed tremendously dilated ventricles with a large third ventricle which lay ine. Suboccipital craniotomy revealed a hemangioblastoma which separated the ar hemispheres and displaced the vermis and tonsils.

e 5.—A 44 year old man gave a 12 year history of occasional momentary attacks of u" feelings. He had never been unconscious or fallen. The attacks were followed eralized sweating. Eighteen months previously he experienced a sudden electric ensation down the right side of the body, face and extremities, and following that ensation of numbness in right side of face and right finger tips which increased in Concomitantly he felt a grating sensation and stiffness of the neck with move- d this was associated with intermittent sharp pain behind the right ear and over t temporal region. Four months later he developed difficulty in swallowing solid d then noted a transient blurring of vision. He stated that when he looked to right, appeared to jump up and down. He had had poliomyelitis at age six with resulting ng and deformity of right foot. A forceps injury at birth produced laceration in cipital area.

mination: A large transverse scar at right occipital area, result of birth injury. leformity of right foot with "frozen" right ankle. Counter-clockwise nystagmus on looking to the right and clockwise on looking to the left. Left facial weakness, palate moving better on left than on right. Slight falling away of right outstretched

upper extremity. Slight dysmetria on finger-to-nose test on right with increased dissociated movement of that extremity. Clumsiness of fingers of right hand in performing fine movements. Right thigh atrophic and muscles below knee weak. Hammer-toes right foot. No ataxia of lower extremities. Heel-to-knee test was well performed, with slight swaying of trunk when in sitting position. Ulnar and biceps reflexes equal and active. Right triceps and patellar reflexes greater than left. Achilles reflex absent on right and diminished on left. Right cremasteric reflex present, the left absent (left testes undescended). Left abdominal reflexes less active than right. Babinski hand sign with bilateral Hoffmann signs. No pathologic reflexes in lower extremities. Corneal reflex absent on right and active on left. Marked hypalgesia over C1–C5 segments on right with slight hypalgesia at same levels on left. Defect extends over right side of face. Sensation to touch diminished in same areas. Less sensitive to cold in cervical segments 3, 4 and 5 on right than on left. Unable to recognize objects placed in either hand, but identifies figure writing on both. Vibration and position sense lost in both hands.

Ventriculography revealed a symmetrical dilatation of the lateral ventricles with third ventricle in midline. A suboccipital craniectomy with cervical laminectomy (C1–C5) uncovered a syringomyelic cavity from the foramen magnum to seventh cervical level.

Case 6.—A woman developed intermittent dull, throbbing aching pain in right neck extending from base of skull to right shoulder in 1928. In the spring of 1932 the pain extended into right upper arm. In January 1933 she noted tingling in finger tips of both hands which progressed so that by May 1933 palms were numb. In May 1933 intermittent episodes of twitching were noted in the muscles of thighs. She burned the left hand in June 1933 and did not feel it. About this time she noted clumsiness in using hands, dropped a cigarette without knowing it, and began using both hands when drinking from a glass. In August 1933 she developed a sensation of tightness in low back and had difficulty in walking. There was a tendency to pitch forward and she veered to left. She became unable to distinguish heat and cold in the left thigh. In October shortly before admission to hospital, she noted a spread of this loss of heat and cold sensation over left side of body, from clavicle downward including left leg. She had marked difficulty in walking especially with right leg which felt weak and wobbly. She also noted marked clumsiness in using right hand and arm.

Examination: Tender to pressure over sixth and seventh cervical spines. Carried head forward. Flexion of neck painful, and when done she experienced "feeling of electricity" down back and shoulders. Cranial nerves normal. No obvious atrophy or weakness in upper extremities and no falling away of outstretched limbs. Clumsy in forming a cone with fingers, and some ataxia in finger-to-nose test on left. No dysmetria. Heel-to-knee tests well done. All other movements of lower extremities well done, but there was weakness to dorsiflexion of right foot and tendency for falling away of right lower extremity when outstretched to 45 degree angle. Marked resistance to passive movements of right lower extremity, which was spastic. Right wrist jerk greater than left, as were biceps and triceps jerks. Right knee and ankle deep tendon reflexes more active on left. Babinski sign on right. Abdominal reflexes present but more active on left. Loss of appreciation of touch from fifth lumbar segment downward on left and on right from fourth to twelfth thoracic segments. Loss of appreciation of temperature sensation as high as seventh cervical segment. Heat sense diminished on left to C4. Pain sensation diminished from 4th cervical downward only on left. Vibration diminished in left upper extremity and in left lower. Joint sensation in toes normal. Numeral writing not tested. Sphincters normal.

Laminectomy on November 16, 1933, revealed a small rounded pinkish-brown tumor inside the dura mater, a meningioma. This was long and narrow and rested on posterolateral surface of spinal cord at C3.

Case 7.—A man aged 36 had noticed tingling and spasms of fingers of left hand for eight years. In the past year he became unable to perform skilled movements with the left

hand, could not tie knots, dropped cigarettes, fumbled with coins in left hand, could not get left hand into back pocket. There was constant numbness of left hand, with weakness and painless twitches of the left arm. There were disagreeable feelings when touching an object, and texture sense was "peculiar."

Examination: Left arm falls away slightly. No motor defects. No ataxia. Left hand smaller than right. All movements possible. Interosseus atrophy on left. Weakness of the abductor digiti quinti on left. Weakness of pronation and suppination. Deep reflexes on left side slightly greater than on right. Abdominal and cremaster reflexes absent. No Babinski sign. Hyperpathic response to touch and pain over left hand. Some diminution of touch over left little finger. Loss of deep sensation, joint, vibration sense in fingers of left hand. Left pupil larger than right. Left stereoanesthesia. Skin writing interpretation normal.

Operation revealed a cellular neurofibroma at C2 on left side, 3 cm. in diameter. Four months postoperatively vibration and joint sense had returned to the left upper extremity, but there is anesthesia involving all modalities of sensation on left, C1, 2, 3, 4.

Case 8.—A woman aged 33 had noted a loss of feeling in right arm, shoulder, back of neck and head four years previously. She was unable to identify pain, touch or position sensation but could recognize heat and cold. During the next year she developed a staggering gait, weakness of right arm and hand, and pain and stiffness in left side of neck. Cervical laminectomy was performed and no abnormal findings were noted. Following operation the symptoms were increased and she later lost sensation in left arm and shoulder. In addition she noted an increase in weakness of right hand with a beginning of intermittent morning nausea and occasional vomiting which was associated with stiffness and pain in back of neck. Six months previously she noted a progressive weakness of right leg and from that time to admission to hospital she had progressive weakness of both arms and right leg. She had fallen several times when attempting to walk.

Examination: Cranial nerves normal. Walked with a staggering unsteady gait, dragging the right foot and veering to the right. Extreme weakness in both upper extremities, the right more than left. Unable to form a cone or to extend the fingers. Heel-to-knee tests were poorly done. Definite atrophy of both upper extremities and great difficulty with skilled movements of hands bilaterally. The finger-to-nose test poorly done, with dysmetria on right, but well done on left. The biceps and triceps reflexes absent, patellar and Achilles reflexes hyperactive. Right patellar and bilateral ankle clonus. Right Babinski sign. Loss of sensation to pain, touch and vibration in both upper extremities. On left this extended over occipital area of scalp and ended at axilla. On right this loss extended to same superior level and inferiorly on chest to fourth thoracic segment. Vibratory sensation partially lost in lower extremities. Complete loss of proprioception in upper extremities and impairment of proprioception in the lower extremities. X-rays of skull and cervical spine not abnormal except for laminectomy defect. Spinal puncture revealed partial manometric block and total protein of 119 mg./per cent.

Operation revealed an intramedullary tumor extending from the fourth ventricle to C3 segment. This tumor proved to be an ependymoma.

Case 9.—A woman aged 59 had noted pain and sensory loss of right half of body of seven months' duration. She developed numbness in the fingers of right hand which gradually progressed to involve the arm, shoulder, gluteal region, legs and finally the face. Pain developed after numbness in upper extremities, but preceded numbness in lower. The pain was described as continuous and deep, like a burning or an ache, aggravated by a fatigue or excitement and partially relieved for short periods by various drugs like empirin. The past history was significant in that she had had a radical mastectomy one year previously for carcinoma.

Examination: Loss or diminution of all sensory modalities in right half of body. Ataxia and dysmetria of right hand. The upper extremity fell away when extended, and seemed to be "lost" when eyes were closed. Biceps, triceps, radial and ulnar reflexes greater

on right than on left. Right Hoffmann sign present and an indefinite left Hoffmann to-knee test poorly done bilaterally, worse on right. Wiggled toes poorly on right. ning ankle clonus on right. Right Achilles reflex more brisk than left and bri clonus on right. Vibration sense absent over right big toe and diminished elsewhe prick and touch lost over the entire right side of the body. Right corneal reflex ished. No recognition of objects placed in right hand. Right optic nerve head blurred; right half of face does not move well. Skin writing lost over right half but normal on left.

Re-examination one week later revealed Babinski sign on right with a right hand sign. Loss of deep pain and pressure on right but no loss on left. Lumbar p showed normal manometric pressures and normal fluid. Psychological tests disc over-responsiveness to stress with more emotionality than normal; there was no ge deterioration but there were some findings of "frontal lobe involvement," as meas these tests.

Electroencephalogram showed much 22 per second activity over frontal lob 6 per second bursts over left hemisphere. Radioisotope test gave normal record. fields were normal. An x-ray of the lung was normal as was x-ray of skull. Imp Metastatic carcinoma, left thalamus.

Case 10.—A man aged 25 had had an embryonal cell carcinoma of right tes which orchiectomy was performed 10 months earlier. Following his operation he x-ray irradiation. He was admitted to hospital eight months later with evident pu and liver metastases for which he received x-ray irradiation. While undergoing th ment he complained of severe epigastric and bilateral abdominal pain. One mo viously he had a sudden onset of sense of numbness of left leg, followed by a w and twitching movements of left leg. Two days later this subjective, constant, s had spread to involve the left buttock. Subjective numbness had moved up to l and mid-chest. Since onset, weakness of left lower extremity had been periodi occurrence. There was no history of bowel or bladder disturbance. X-rays of spi negative.

Examination: Skin icteric and pale. Liver enlarged to 8 cm. below costal marg skin over abdomen was discolored from irradiation. Right testicle absent. Large no lymph glands in both inguinal regions. Favored left lower extremity when walki localized area of tenderness to percussion over calvarium. No cranial nerve abnor Veins of fundus greatly distended. The upper extremities were held unsteadily, b was no definite pastpointing or falling away. Definite ataxia on finger-to-nose test, e on left. Lower extremities moved well. The tibialis phenomenon was good on r poor on left. Marked hypotonia in left ankle joint. Heel-to-knee test better on r not well done on either side. Cotton touch, pain, temperature and vibratory sens preserved and no difference on the two sides. Number writing on the skin revealed ous mistakes on left lower extremity while the rest of body remained completely Biceps, triceps, radial and ulnar reflexes brisk and equal. Patellar response active side but greater on left than on right. Achilles reflexes brisk and questionably mo on right. Exhaustable ankle clonus on left. No pathologic reflexes elicited; plantar r normal. No astereognosis, apraxia or aphasia.

The patient had two severe gastric hemorrhages and developed a septic fe pulmonary congestion. Two Jacksonian seizures involving the left side of body occu day before death and on last day there were several other similar seizures. Final grand mal seizure with coma and death.

Autopsy revealed metastases from right testicle to lungs, liver and aortic a lymph nodes with an extension into the duodenum and hemorrhage into the ga tinal tract. The brain showed an extensive hemorrhage over right cerebrum with

TABLE II

SUMMARY

Location of Lesion	*Number of cases*	*No. with total touch sense loss*	*No. with ataxia*	*No. with position sense loss*	*No. with vibration sense loss*	*No. with loss of "object-in-space" awareness*	*No. with loss of "numeral writing" awareness*
High Cervical cord	6	0	6	6	6	6	0
Thalamus	1	1	1	1	1	1	1
Parietal Cortex	1	0	0	0	0	0	1

dilated vessels over the right cerebral cortex. A tumor, made up of four nodules, was found in the right parietal cortex.

Table 1 demonstrates the important symptoms of patients with cervical cord lesions, none of whom could recognize an object placed in one or both affected hands. In three instances both limbs were affected. This would rule against a cortical or subcortical lesion and would place the pathology where the pathways run closely together, in the upper spinal cord or lower brain stem.

In the remainder, however, only one limb was affected. In every instance position sense was impaired and the limb was ataxic with the usual pseudo-athetoid movements of a part which has lost deep sensibility. Vibration was markedly impaired or absent in every case, but figure-writing appreciation was preserved in the four unilateral cases where it was tested. Graphesthesia was preserved in the two cases of bilateral lesions where it was tested and where position, vibration and spatial perception were absent. In all cases where figure writing was preserved, there was preservation of light touch or no loss at all.

Other signs like local muscle atrophy, weakness, reflex changes and papill-edema helped identify the cervical level.

In contrast, case 9, with a metastatic lesion in the left thalamus, also had a markedly disturbed right arm and hand. She "lost" objects placed in the hand. She could feel no sensation there, deep or superficial, and paid no attention to exteroceptive stimuli except stroking, which gave her intense discomfort. The entire right half of the body "burned" as is often the case in thalamic lesions. She had no concept of figures written in her right hand. The left was very accurate in recognizing the numbers.

In further contrast was case 10, a 25 year old man with a metastatic carcinoma of the testicle. The lesion was exquisitely placed in the right parietal lobe. His sensory tests were normal except for the inability to recognize figures written on his left leg, the site of initiation of subsequent Jacksonian seizures. He also had a minimal ataxia on finger-to-nose test on the left. Vibration sense, as expected, was intact as were pain, touch and temperature. He had no astereognosis in the left hand, and even figure-writing was intact here. The lesion lay high and medially in the parietal lobe.

DISCUSSION

The data presented here bear out much of what most investigators have described, but are at variance with others (table 2).

High cervical cord lesions produce profound disturbances in spatial relationships of the hand and arm so that objects placed in the hand are not recognized. This is stereoanesthesia. In addition, the unwatched limb is so ataxic and clumsily placed that it acts athetotic (pseudoathetosis). Vibration and position sense are markedly impaired to absent, but figures written on the affected limb are readily recognized. Since in our cases there was some preservation of light touch, the possibility is suggested that these stimuli reaching the parietal cortex might be synthesized into a recognizable figure. Our findings are in counterdistinction to those of Wartenberg[18] and others who found the early loss of the "numeral sign" as a good spinal localizing symptom, long before other modalities of deep sensibility changed. We cannot explain the divergence of findings. The sign, however, requires an intact parietal cortex to synthesize direction and length of line drawn on the skin into a figure which is identified with a memory image of a number. This ability may be lost at a cortical level where vibration appreciation is unaffected and where a clear cut astereognosis is not yet present. A thalamic lesion interrupts all modalities of sensation so that no integration of sensation at a higher level may occur. The hyperpathic responses which may ultimately reach the cortex in some cases are a product of removal of cortical control from the lateral thalamic areas.[20]

CONCLUSIONS

1. Interruption of the posterior columns at a high cervical level produces profound disturbances in deep sensibility in one or both of the upper limbs.

2. It is recommended that the spatial appreciation defect so produced be called stereoanesthesia since the defect is in conduction, and that the term astereognosis be used exclusively to designate instances in which there is no defect in conduction, as in parietal lobe lesions.

3. High cervical stereoanesthesia is usually accompanied by loss of pallesthesia and kinesthesia but graphesthesia may be preserved.

4. Thalamic lesions obliterate or disturb all modalities of exteroceptive sensation, hence pallesthesia, kinesthesia and graphesthesia are equally affected.

5. Parietal cortex lesions affect functions dependent on spatial orientation, hence produce a loss of figure-writing interpretation (graphagnosis or agraphognosis) and loss of object in space recognition (astereognosis), while a non-space orienting function, vibration sense, is spared.

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This mode of instituting blood-letting also guards us against some terrible mistake, and yields an important diagnosis. There are some diseases so similar to encephalitis, that the most experienced physicians cannot be absolutely certain what a given case may be. These cases would be brought to a fatal issue if the same quantity of blood were withdrawn, as is both proper and necessary in encephalitis. Adopt the rule for blood-letting which I have proposed, and you will be saved from the danger of inefficient blood-letting in the case of inflammation, and of undue blood-letting in the other cases, so similar to it in appearance, yet so different from it in reality! you will also possess an accurate and important source of diagnosis. If it be inflammation, much blood will flow before the lip becomes pale; if it be of the other kind of disease to which I have alluded,—such, for example, as delirium tremens and certain congeneric affections—very little blood will flow before that event occurs!

Topical blood-letting is appropriate in cases in which some symptom or symptoms remain, and we dare not deplete the system further.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases,* published in 1876.

Background Illumination and the Visual Threshold in Hemianopic Areas

Morris B. Bender, M.D. and Howard P. Krieger, M.D.

That light may be perceived and localized within areas described as anopic by conventional perimetry was demonstrated in a previous study.[1] To elicit these phenomena, the defective field had to be examined in darkness with a luminous target. Under similar conditions, changes in the absolute visual threshold could also be measured in these defective areas. Dark adaptation curves constructed from such data were found to differ from the normal quantitatively and qualitatively.[2] The quantitative difference was a rise of about 300 to 1500 times in the threshold of the defective areas as compared to the normal areas. The qualitative difference was most evident as an absence of the plateau which appears in the early part of a normal dark adaptation curve. This plateau has been interpreted as the cessation of cone adaptation while the subsequent fall in threshold has been attributed to the adaption of the rods alone.

These investigations[5] also demonstrated that changing the illumination of the background affected the perception of the target located in the so-called hemianopic field.[1] This paper describes an attempt to quantify the relationship between background illumination and target perception.

MATERIAL

This study was carried out upon two hemianopic patients. The first, A.F., aged 39, had a surgically removed subdural hematoma. Before operation there was a right third nerve palsy and a left homonymous hemianopia. Postoperatively the hemianopia remained. The retinae were at all times normal upon ophthalmoscopic examination. Routine perimetric examination showed the hemianopia with about 8° of macula sparing. However, examination of the defective fields with a luminous target of threshold value in a dark room

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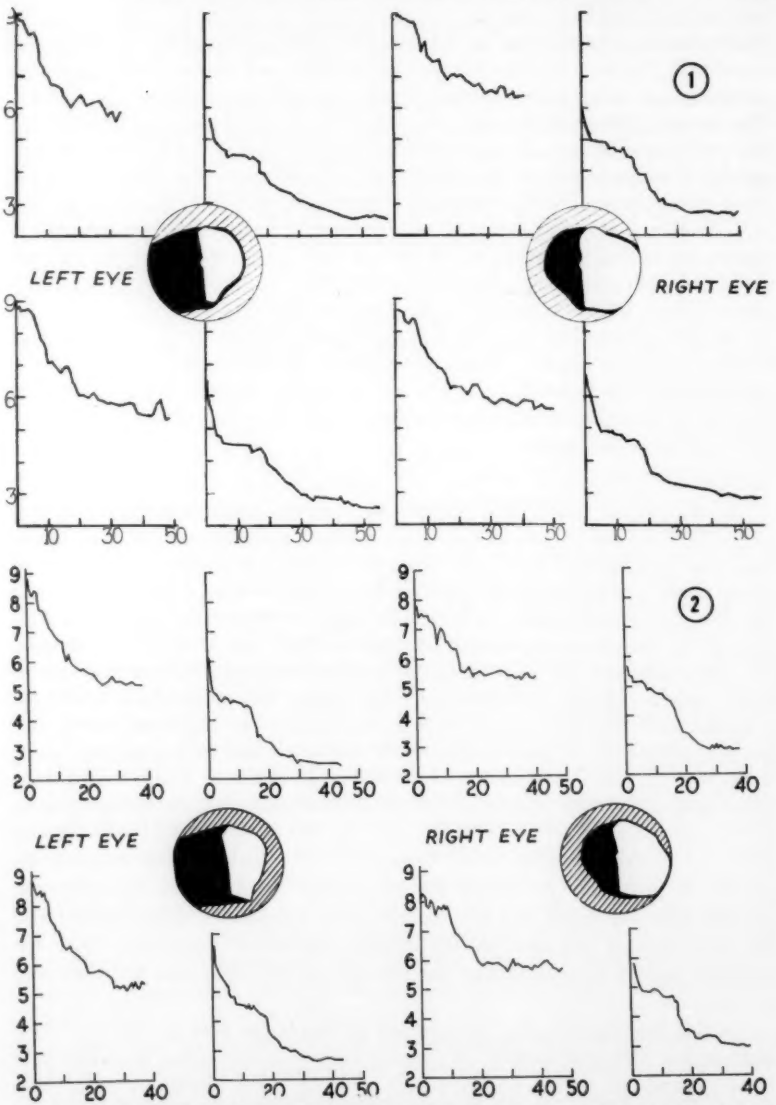

FIG. 1. Dark adaptation curves and perimetric fields of A.F. Each curve was measured at 20° from the fovea along the 45° meridian of the four quadrants of each eye. Abscissae—minutes. Ordinates—logarithm of the absolute visual threshold in micromillilamberts. The blacked out areas of the perimetric fields represent the defect.

FIG. 2. Dark adaptation curves and perimetric fields of M.F. Loci of measurements, abscissae and ordinates as in figure 1.

showed some visual function as far out in the field as 90° along the horizontal meridian.[1] Figure 1 contains the perimetric fields and sample dark adaptation curves of analogous points in the normal and defective fields of this patient. The second patient, M. F., aged 42, presented a mild right-sided paresis and bilateral hyperreflexia. A right-sided subdural hematoma was removed surgically. Postoperatively, a left homonymous hemianopia was found; all other signs disappeared. Ophthalmoscopic examination revealed no retinal pathology. Figure 2 contains this patient's perimetric fields and dark adaptation curves for analogous points in his normal and defective fields. In this case some visual function could also be demonstrated along the horizontal meridian of the defective field as far out as 90° from the fixation point.[1]

In both patients the histories, symptoms and signs led to the clinical diagnosis of cerebral lesions. Perimetric findings indicated involvement of the optic pathways beyond the optic chiasm. Thus, any changes in visual function may be presumed to stem from alterations in the function of the visual pathways and/or visual cortex.

METHOD

In the present study, the target was a circle subtending 2½° of retinal angle 20° from the fixation point. The head was immobilized and ocular fixation was maintained with a just visible pin point of red light. The source of target illumination was Wald's portable adaptometer[3] with a white bulb (G.E. No. 55), the light of which was passed through a milk glass screen. The brightness of the target was controlled by neutral filters and a variable resistance. The latter changes the spectral characteristics somewhat, but for the present work such a shift was unimportant. The target was exposed for 1/25th of a second each time the patient tripped the shutter. The brightness of the target was measured in micromillilamberts and expressed in logarithmic units. Time was measured in minutes beginning at an arbitrary point before complete dark adaptation was achieved. The threshold could be determined as often as twice a minute. Essentially, this was the method used by Hecht and Shlaer to measure absolute visual thresholds.[4] This measurement was accomplished by gradually increasing the target intensity between successive exposures until the target just became visible to the patient. This method had the advantage of not affecting the absolute threshold appreciably since the exposure time was so short and the intensity of the light was just threshold or less.

In this investigation the background of the target was of uniform black cloth of low reflecting quality. It covered more than the entire binocular field of vision and was within a room which could be made absolutely dark. This background could be illuminated by a bulb placed just above the patient's head in such a way as to light the entire visual field almost evenly. When illuminated at the highest intensity used in this study, the albedo of the background was such that it reflected less than 0.1 ml. measured at 27 cm. from the

cloth (the distance of the eye from the cloth) as determined by a Weston foot candle meter. A variac was used to control the brightness of the background illumination.

The patient was seated in the completely dark room until there was no longer any significant change in his absolute visual threshold. After determination of this threshold, the background was suddenly illuminated and the threshold determined under the new conditions. This procedure was then repeated for various background illuminations.

It should be noted that this procedure measured two types of thresholds, the absolute and the differential. The absolute threshold, at any given time, was determined by finding the minimal intensity required for the patient to become aware of the sensation of light against a background of absolute darkness. On the other hand, the differential threshold was determined in the presence of a background illumination. Under these conditions the patient was asked when he first became aware of a sensation of light in addition to the background illumination. This sensation was created by gradually raising the intensity of the target now surrounded by the illuminated background. The differential threshold was, therefore, the minimal target intensity required for the patient to become aware of a sensaton of light in addition to and minimally brighter than a given illuminated background. Or it may be said that in determining the differential threshold the patient was required to discriminate the target from the illuminated background. In determining the absolute threshold, the patient was required to make a distinction between a target of minimal intensity and absolute darkness.

Our interest was in the effect of illumination of the background upon the visibility of the luminous target within the so-called anopic field. To relate the alterations in the visual threshold to changes in the background intensity, the latter was measured as millilamberts incident upon the target since, as noted, the albedo of the cloth was low. It was observed that the change in visual threshold upon increasing background illumination bore a simpler mathematical relationship to the voltage activating the source of illumination than to the degree of illumination expressed in millilamberts. This relationship between volts and background illumination was logarithmic; 20 volts corresponded to approximately 0.0002 ml., 30 v. to 0.15 ml., 40 v. to 0.4 ml., 50 v. to 1.5 ml., and 60 v. to 4.0 ml. as determined by the Weston foot candle meter and MacBeth Illuminometer. Therefore, the degree of background intensity was also expressed in terms of the voltage applied across the source of its illumination.

Changes in the visual threshold were measured in micromillilamberts and any rise in threshold was measured in relation to the absolute visual threshold of the area under consideration when this area was fully dark adapted.

In this work one other parameter was varied; the pupil was either dilated with homatropine or allowed to react freely.

Previous studies were used as a control for the absolute thresholds of the

fully dark adapted areas.[2] These thresholds were the same in this and the previous studies. Furthermore, in the normal areas of the two patients and in the one normal subject used as a further control in this work, these thresholds were within the limits of normality found by Hecht[4] and by Mandelbaum.[5] In the case of A. F. the normal area of one eye was an additional control for the defective area of the same eye. Such a control obviated the necessity of a series of patients for it allowed us to compare a defective area with an homologous normal area within the same eye. Homatropine was used to evaluate the effects of pupillary contraction.

RESULTS

The results are presented graphically in figures 3, 4, and 5. The ordinates are intensity measured in $\log_{10}$ micromillilamberts, the abscissae time and below each abscissa will be found bar graphs indicating the duration of illumination of the background at specific intensities expressed in volts.

In figure 3 are presented the data for the control subject with homatropine. As the illumination of the background increased, so did the differential threshold. For each increase of 10 volts this threshold rose above the absolute threshold approximately $\log_{10}$ 0.5 to 0.6 μml. This rise in threshold occurred witihn one minute. The fall in the absolute threshold, after removing the background illumination, was found to be slower the higher this preceding illumination. This last observation was in accord with Hecht's study of rod adaptation following light adaptation with intensities below that which will affect the cones.[6]

In figure 4 are the graphs for patient A.F. In figure 4a are those for her normal field without homatropine. The results are the same as for the control subject except that for each increase of 10 volts in the source of background illumination the rise in threshold was about $\log_{10}$ 0.45 μml. The rapid rise and the rapid or relatively slow fall in threshold was again noted.

In figure 4b are the graphs for A.F.'s defective field with and without homatropine. The most significant observation made with the target in the defective field was that raising the background illumination could lead to the subjective disappearance of the target. In the case of A. F. a background illumination greater than 50 volts (1.5 ml.) without homatropine or 40 volts (0.4 ml.) with homatropine resulted in the subjective disappearance of a target of $\log_{10}$ 7.2 μml, the brightest available in this study. This disappearance occurred within 10 to 30 seconds.* In addition, it was observed that there was more fluctuation of the threshold in the abnormal fields, a finding previously described.[1,2] Two similarities between the normal and defective areas were noted: (1) upon illuminating the background, the rise to the differential threshold was rapid, while upon returning to darkness, the fall to the absolute threshold was slower the higher the preceding background intensity, and (2)

*Similar observations were reported in an earlier study[1,2] and parallel observations have been described for somesthesis under the terms extinction.[7,8]

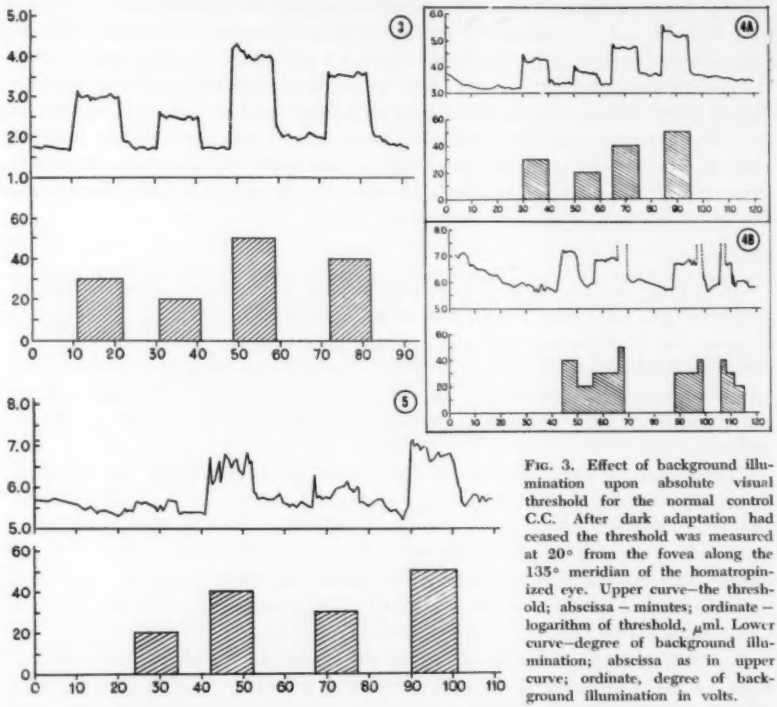

FIG. 3. Effect of background illumination upon absolute visual threshold for the normal control C.C. After dark adaptation had ceased the threshold was measured at 20° from the fovea along the 135° meridian of the homatropinized eye. Upper curve—the threshold; abscissa – minutes; ordinate – logarithm of threshold, μml. Lower curve—degree of background illumination; abscissa as in upper curve; ordinate, degree of background illumination in volts.

FIG. 4a. Effect of background illumination upon the absolute visual threshold in the normal field of A.F. After dark adaptation ceased, threshold measurements were made at 20° from the fovea along the 135° meridian of the left eye not treated with homatropine. Abscissas and ordinates as in figure 3.

FIG. 4b. Effect of background illumination upon the absolute visual threshold in the hemianopic field of A.F. After dark adaptation ceased, threshold measurements were made at 20° from the fovea along the 225° meridian of the left eye. Homatropine added at the 68th minute. *Note*: (1) that the threshold curve is interrupted for 3 intervals representing the subjective disappearance of the target and (2) that the thresholds in this defective area are higher than in the analogous normal area depicted in figure 4a. Abscissas and ordinates as in figure 3.

FIG. 5. Effect of background illumination upon the absolute visual threshold in the hemianopic field of M.F. After dark adaptation ceased the threshold measurements were made at 20° from the fovea along the 225° meridian of the right eye to which homatropine had been added. Abscissas and ordinates as in figure 3.

homatropine caused only a slight general lowering of both thresholds on the intensity axis.

In figure 5 are the graphs for the hemianopic field of patient M. F. after ocular instillation of homatropine. The results were qualitatively the same as in patient A. F. but subject to greater fluctuation. For M. F., with homatropine, when 20 v. created the background illumination the differential threshold

was 0.2 log unit higher than the absolute threshold of the fully dark adapted eye; with 30 v. it was about 0.4 log unit higher. However, 60 v. rendered the $\log_{10}$ 7.2 μml target subjectively invisible. In addition, it was observed that the differential threshold, expressed in log units of micromillilamberts, had an almost linear relationship to the degree of background illumination, expressed in volts. However, the fluctuation of the threshold was too great in this patient to warrant an absolute quantitative statement. In this case there was again the abrupt rise in the threshold upon illuminating the background and the lower fall upon return to complete darkness.

CONCLUSION

Increasing the background intensity of a luminous target perceived within a hemianopic field may render the target subjectively invisible. That is, increasing the background illumination beyond a specific point may make the defective field appear "blind." The point at which this extinction of the visual target occurred was apparently an expression of individual difference among the patients and the difference in brightness between the target and background.

The point of extinction could have been predicted given the absolute threshold, the degree of differential threshold increase for each unit rise in background illumination and the target brightness. For example, in patient A. F., without homatropine, when 40 v. were applied to the source of background illumination the differential threshold was $\log_{10}$ 7.15 μml. Our data indicate further increase of 10 v. would be expected to raise the threshold to about $\log_{10}$ 7.5 to 7.9 μml., or beyond the brightness range of the target. Actually with a background illumination corresponding to 50 v. the target of $\log_{10}$ 7.2 μml. was not seen. With homatropine, the same things held true; with 30 v. the differential threshold was $\log_{10}$ 7.1 to 7.6 μml. and with 50 v. it would be $\log_{10}$ 7.9 to 8.3 μml. As could be predicted our target of $\log_{10}$ 7.2 μml. maximum intensity was always seen by A. F. when treated with homatropine at a background intensity corresponding to 30 v. and 40 v. but never to 50 v.

The foregoing observations show that a hemianopia, resulting from a lesion beyond the chiasm, does not always mean a complete loss of visual function in the scotomatous region. The intensity of the hemianopia depends in part on the conditions of testing, one of them being background brightness. Thus when background brightness was reduced to zero and dark adaptation was allowed to occur, the demonstration of some visual function became possible. If then an increasing background illumination was created the above described extinction took place at a critical point.

The occurrence of this target extinction when the background illumination exceeded a critical value raises the question of whether the scotoma found upon routine perimetric examination should be interpreted as related to lack of enough difference in brightness between the target and background. The data of this investigation indicate that such an interpretation is valid. Furthermore, an anopia may be induced in normal subjects by suddenly raising the

background illumination to 1500 ml. Under such conditions, a target of intensity $\log_{10}$ 9 μml. was found to be momentarily invisible.

The results of this study also lend themselves to comparison with the investigations of the phenomena of sensory extinction.[7,8] Extinction is a condition wherein the simultaneous introduction of two stimuli into a sensory field results in the subjective disappearance of one of the stimuli. This is most readily demonstrated if one of the stimuli is applied to a defective part. In other words, when two simultaneous stimuli are applied, one to an intact area (i. e., that of low threshold) and the other to a defective area (i. e., that of high threshold) the response is as if only one area, that of low threshold, were functioning. The analogy between these observations and those of the present study can be drawn if conditions of stimulation in each are viewed from the Gestaltist standpoint.

Studies in Gestalt psychology have demonstrated that visual perception can be considered in terms of figure-ground relationship. What is perceived depends in part on what is placed before the eyes or the stimuli originating from the total field of vision. This has been termed as the stimulus field. In the stimulus field there is a figure and background, each of course acting as visual stimuli.

In our experiments of measurement of absolute visual threshold in darkness, the total or stimulus field was a figure (luminous target) against a background of "absolute" darkness or no visual stimulation other than that which originated from the figure. When we measured the differential threshold, the stimulus field was either a uniformly illuminated field (stimulus backgound) or a figure (visual target) against this uniformly illuminated background. In the latter situation the perception of stimulus figure was influenced by the change in stimulus background. As the background illumination was increased to a critical point the patient's ability to perceive the stimulus figure in the defective part of the field of vision was decreased. These results might be interpreted as extinction of a percept (visual target) evoked by a stimulus in a defective part of the field (hemianopic region) as soon as a simultaneous stimulation is made in another part of the field of vision, namely the illumination of the background. In short, there was extinction of visual target by simultaneous stimuli arising from a background. The more intense the stimuli in the background, the less perceptible was the target until a critical point was reached and extinction occurred.

SUMMARY

1. Patients who presented an homonymous hemianopia when examined under daylight illumination could see a small luminous target in these apparently blind areas provided the background illumination was almost eliminated. Raising the illumination of the background was found to raise the differential threshold in apparently hemianopic areas as measured with a luminous target in a dark room.

2. The degree of rise in the differential threshold was the same in both the normal and defective areas, except that in the anopic areas a critical point was found beyond which a rise in the background illumination resulted in subjective disappearance of the target.

3. After removal of the background illumination, the rate of dark adaptation was found to vary inversely with the intensity of the preceding background illumination. This was true of both normal and abnormal areas of the field of vision.

4. These results were considered in relation to the difference in absolute threshold between the normal and defective half fields and interpreted in terms of simultaneous stimulation of analogous normal and defective sensory fields and in terms of figure-ground relationships.

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The ophthalmoscope consists essentially of a concave mirror perforated in the centre, and of a double-convex lens. Several modifications of this arrangement are in use, but the simplest instrument is, in my opinion, the best, and this is Liebreich's.

It consists of a polished steel mirror about one and three quarter inches in diameter, concave, and perforated in the centre by a hole about the one-twelfth of an inch in diameter. The edges of this aperture are bevelled so as to afford as little obstacle as possible to the passage of the rays of light to the eye of the observer.

Ophthalmoscopic examinations require the observer to possess a very thorough acquaintance with the anatomy of the eye and also with the science of optics. Unless these qualifications are enjoyed, it will be much better to send the patient to a competent ophthalmic surgeon for an examination, than to rush to hasty conclusions based on the most thorough ignorance. The real value of ophthalmoscopy in diseases of the nervous system is in danger of being disregarded through the sciolism of pert pretenders, who read papers and write memoirs without ever having seen the optic disk to recognize it.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

Bodily State in Injuries of the Spinal Cord

Herman Chor, M.D., Isidore Finkelman, M.D. and Herman Blustein, M.D.

In injuries of the spinal cord, most attention has been given to the well-known resultant disturbances in motion, sensation, reflexes, bowel and bladder function, and trophic state, more particularly bed sores.[1] In addition to these, however, there are alterations in other bodily functions such as cardiovascular regulation, glucose metabolism, water metabolism, temperature regulation, gastrointestinal activity, which deserve recognition and further study.[2] The nervous regulation of various bodily functions requires that the influences from centers in the cerebral cortex, diencephalon and brain stem be transmitted through connections and pathways of the autonomic nervous system. Many of these influences reach the viscera or tissues to be regulated through the spinal cord, and lesions of the spinal cord may result in an interruption of these influences from the higher centers. In addition, activities arising from the isolated distal segment of the spinal cord may result in abnormal visceral responses. This is clearly seen in studies on blood pressure regulation giving rise to postural hypotension and reflex hypertension.

BLOOD PRESSURE ALTERATIONS

A study of the basal blood pressure of 353 patients with injuries of the spinal cord showed an average blood pressure of all cases of 116.0 mm. systolic and 73.1 mm. diastolic, with a pulse pressure of 42.9 mm. The variation was rather wide but in keeping with the blood pressure findings in healthy young men of a similar age group as reported by Brouha and Heath[3] in 1943. It may be noted that patients with a cervical cord lesion (C3–T4) show a tendency toward a lower blood pressure. In this group of 36 patients the average pressure was 110.1 mm. systolic and 69.3 mm. diastolic, with a pulse

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pressure of 40.8 mm. In a few of these quadriplegic patients the blood pressure readings were as low as 78 mm. systolic and 50 mm. diastolic.

Although the basal blood pressure may appear to be quite normal, when demands calling for regulation of blood pressure are placed upon the cardiovascular system, strikingly abnormal responses may be seen. It is not uncommon for a patient with a severe spinal cord injury to "black out" when attempting to sit up, unless special precautions are taken. This is due to orthostatic hypotension. Of 37 patients with cervical and upper thoracic cord lesions, 56 per cent showed this tendency; ten definitely "blacked out," seven did so only shortly after the injury, and four noted dizziness and faintness without loss of consciousness. Of 114 thoracic cord cases, 14 per cent showed this tendency; three definitely "blacked out," eight did so only shortly after the injury, and five did so after long fever or sickness. Of 57 lumbar and cauda lesions, 4 per cent showed this tendency.

In a previous publication,[2] findings of orthostatic hypotension in ten cases of physiologically complete lesions of the cervical spinal cord have been reported. Upon tilting from a horizontal to a vertical position the basal systolic blood pressure, with a range of from 80 to 150 and an average of 114 mm. of mercury, fell so precipitously that the pressure could not be read by auscultatory methods and the pulse could not be palpated. So severe was the ensuing cerebral anemia that unconsciousness resulted in eight patients. A disturbance in the proper function of the sympathetic nervous system is responsible for this inability to maintain blood pressure in the erect position.

In the normal individual, distention of the external sphincter and of the rectum results in an increase in blood pressure. Because of regulatory impulses from above, this increase is slight and of short duration. It has been noted that when the spinal cord is severely injured, striking rises in blood pressure may result from rectal distention. Clinically it has been observed that following an enema, such a patient may show signs of acute distress, associated with a marked hypertension. Sweating, subjective weakness, nausea, severe headache, dizziness, vomiting, palpitations and chills are frequent symptoms. At times the patient may even "black out." Of 26 patients with cervical and upper thoracic cord lesions, seven, or 27 per cent, reported some disturbance; four, or 15 per cent, actually "blacked out," one did so on occasion, and two felt dizzy and faint. Of 105 patients with thoracic cord lesions, 12, or 11 per cent reported some disturbance; six, or 5.7 per cent actually "blacked out," and six became dizzy and weak. Of 51 patients with lumbar and caudal lesions, no patients "blacked out," and only three patients complained of getting dizzy or faint when given enemas.

Alteration in blood pressure has been produced experimentally in patients with lesions of the cervical spinal cord by distending the rectum with a balloon. Rises as high as 120, 80, 60, 58, and 52 mm. of mercury resulted, with associated symptoms and signs similar to those following an enema. This reflex hypertension is due to the fact that regulatory impulses fail to reach the

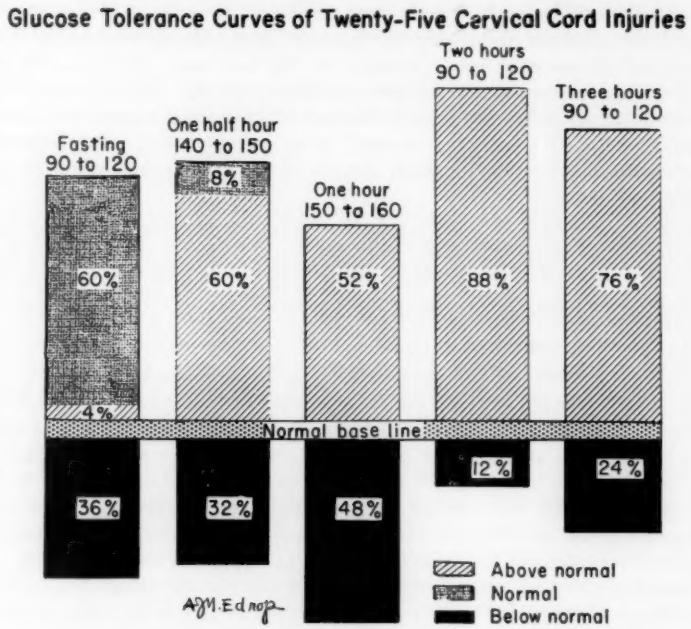

FIG. 1.

thoracico-lumbar outflow. A similar reflex hypertension results from distention of the urinary bladder.

DISTURBANCES OF CARBOHYDRATE METABOLISM

Ever since the discovery by Claude Bernard in 1858 that puncturing the floor of the fourth ventricle gives rise to a marked but temporary hyperglycemia with glycosuria, it has been known that the nervous system plays a role in glucose metabolism. Bernard reported that the impulses bringing about these changes were mediated by the spinal cord and the splanchnic nerves, which he recognizd as sympathetic strands. Since then it has been shown that experimental lesions of the hypothalamus can also cause glycosuria and hyperglycemia. In severe lesions of the spinal cord it would appear likely that the interruption between the central regulatory centers and the peripheral autonomic system might result in alterations in glucose metabolism.

Oral glucose tolerance tests were done in 25 patients with cervical cord lesions. As shown in figure 1, the fasting blood sugar is approximately normal (60 per cent normal, 4 per cent above normal, and 36 per cent below normal). The half hour specimen, however, shows only 8 per cent to have

normal values; 60 per cent are above normal, and 32 per cent below normal. In the hour specimen there were no normal values; 52 per cent were above normal and 48 per cent below normal. In the two hour specimens, 88 per cent were above normal and 12 per cent below normal. In the three hour specimen also, none had returned to normal values – 24 per cent were below normal; 76 per cent were above normal. In no case was there any glycosuria, the renal threshold remaining high despite blood sugar values between 160 and 180 and above.

In these cases in which carbohydrate metabolism was studied, there were no clinical signs of specific disorder of the liver, pancreas or adrenals. It is suggested, therefore, that the abnormal findings are due to failure of inhibitory or excitatory impulses reaching the peripheral autonomic nervous system.

ABNORMALITIES OF HUNGER AND THIRST

Hunger was present in all patients with the same intensity as prior to the injury. Eighty-one per cent ate the same amount of food and 19 per cent ate less food than before the injury. In 95 per cent the sensation of fullness after eating was present, and in 5 per cent it was absent; 33 per cent had discomfort after missing a meal, and 67 per cent experienced no discomfort. In 62 per cent the appetite was stimulated by the sight of food, and in 38 per cent the appetite could not be psychically stimulated; 90 per cent enjoyed eating, and 10 per cent did not experience any pleasurable sensation from eating.

Nausea, for any reason, was present in 75 per cent of cases. It occurred frequently as a result of the distention of the rectum caused by retained feces and by enemas. It was also produced by illness, fever, bladder spasm, duodenal ulcer, unpleasant odors, and presentation of food. Its production by distention of rectum speaks for the integrity of a vagal reflex.

Hiccoughs occurred in many patients as the result of eating or drinking too fast. They were also noted after alcoholic excess and in relation to spasm of the bladder.

All patients had thirst sensations at times, but thirst was less frequently experienced than before the injury. The amount of water required to satisfy thirst ranged from 250 to 750 ml. There was a greater intake of water during hot weather, and some patients were awakened at night to satisfy their thirst. The frequency of daily intake of water ranged from every 15 minutes to every three hours. The normal water intake under conditions of average temperature, humidity and diet, is 2500 ml., of which 1000 ml. is in the form of beverages, such as water, milk, coffee, etc. In the patients with severe spinal cord injuries, the fluid intake was generally increased over the normal. Some patients consumed as much as 12,000 ml. a day. This increase was especially demonstrated during hot weather.

Although the more pronounced instances of polydipsia occurred among the patients with lesions of the cervical spinal cord, it was also noted in lesions of the thoracic cord, the greater number occurring in those with lesions at or above T9 segment. The range of the cases with injury of the thoracic cord

was from 1700 ml. to 7660 ml. with a median of 4020 ml. The range in those with cervical cord lesions was from 2100 ml. to 12,000 ml. with a median of 5440 ml.

These findings imply that diabetes insipidus may occur in lesions of the cervical and upper dorsal segments of the spinal cord, due to disturbance in autonomic reflex function.

ALTERATIONS IN WATER METABOLISM

The normal value for the ratio of quantity of day urine to that of night urine should be at least 3.0. In injuries of the cervical spinal cord the average ratio was 0.72 for complete lesions and 0.91 for incomplete lesions. None had a normal ratio.

In the concentration and dilution test the high specific gravity range of the urine for concentration should be 1.025 in at least one specimen, and for low specific gravity dilution range in at least one specimen, 1.003. In 27 patients with complete cervical cord lesions the high specific gravity range was from 1.007 to 1.026; only three or 11 per cent were over 1.025; 13 or 49 per cent were over 1.020; 14 or 51.8 per cent were under 1.020; and three or 11 per cent under 1.010. In 21 patients with incomplete lesions of the cervical spinal cord the highest specific gravity ranged from 1.008 to 1.036. Only three or 14 per cent were over 1.025; six or 28 per cent were over 1.020; 12 or 57 per cent were under 1.020; and three or 1 per cent were under 1.010.

In 27 patients with complete cervical cord lesions, 13 or 48 per cent had a normal dilution—1.003 or less. The range of the low specific gravity was from 1.002 to 1.008. Of 21 patients with incomplete lesions of the cervical spinal cord, nine or 49.9 per cent had a normal dilution—1.003 or less. The range of dilution specific gravities was from 1.002 to 1.007.

Although there is almost a reversal in the day-night ratio and a defect in the function of concentration, dilution is normal in approximately 50 per cent of the patients. There were no significant differences between complete and incomplete lesions.

In 13 patients with complete thoracic cord lesions there were three or 23 per cent with a normal day-night ratio; ten or 77 per cent had a ratio below normal, with an average of 1.02. In the three cases with incomplete thoracic cord lesions, there was an average ratio of 1.12; none were normal. However, the ratio in thoracic cord lesions is significantly greater than in cervical cord lesions, indicating a milder degree of functional impairment of the kidney.

In 13 patients with complete cord lesions none had normal concentrations. The range of specific gravity was from 1.006 to 1.020; only three or 22 per cent had a specific gravity of 1.020; ten or 78 per cent were under 1.020. All of the three patients with incomplete thoracic lesions had a specific gravity in the concentration specimens of 1.011.

GASTROINTESTINAL MOTILITY

An analysis of motility of the gastrointestinal tract of patients with cervical

spinal cord lesions, determined by barium meal roentgen studies, showed that the barium reaches the hepatic flexure of the colon in four hours. This is within normal limits. Excretion of charcoal, however, is delayed as long as 18 days. This indicates stasis in the colon and rectum, inasmuch as the first parts of a charcoal meal appear in from 16 to 24 hours after ingestion and the last traces are found in from 36 to 48 hours after ingestion in normal man.

GALLBLADDER EVACUATION AND CONCENTRATION

All of the 20 patients tested for evacuation of a radio opaque dye showed normal evacuation and concentration.

DIARRHEA

Although it has been stated that diarrhea is rare in patients with spinal cord injuries, it was frequently seen in our group as a result of dietary indiscretion, cathartics, other drugs, and disease.

WEIGHT

The loss of weight which was constantly found in our patients with spinal cord injuries deserves mention. Among 86 cases reviewed, the loss of weight ranged from 10 to 120 pounds. The mean loss of weight was 55.6 pounds. Nearly 5 per cent lost 70 or more pounds. The time when the peak loss of weight occurred ranged from one month to one year, with the exception of four who continued to lose weight. The mean time was five months. In one case there was a loss of 70 pounds in the first five weeks. Some of the loss of weight was regained as a result of symptomatic treatment for the physical well being of the patients. The range of weight regained was up to 90 pounds, with a mean of 28.71 pounds. Five patients regained no weight but did not continue to lose, and four continued to lose weight. Four gained more weight than they had lost. The terminal loss of weight ranged from none to 80 pounds, with a mean of 31.56 pounds. There was no correlation between level of the lesion or injuries of war and peace. In a small number of cases ultimately having significant recovery of motion and sensation, the initial weight loss was less than in other cases.

POSTMORTEM STUDIES

Postmortem studies have revealed changes in many organs of the body in addition to those primary in the spinal cord.

In the 11 cases which came to autopsy, gross pathologic findings occurred in the following organs listed in order of frequency: in the lungs, pathologic changes were found in 11 cases; in the liver, ten cases; in the kidneys, nine cases; in the spleen, eight cases; in the bladder, eight cases; in the skin (decubiti), seven cases; in the prostate, five cases; in the heart, five cases; in the stomach (gastritis, ulcers), three cases; in the testes, three cases; in the large intestines, two cases; in the small intestines, one case; and in the esophagus (varices), one case.

It is interesting to note that amyloidosis was found in three cases of traumatic paraplegia. In all three cases both the liver and spleen were involved, and in one of these the testes also showed amyloidosis with complete absence of spermocytes.

The cause of death in spinal cord lesions has been usually attributed to infection, especially of the urinary tract and terminally of the lungs. In practically all cases of injury to the spinal cord, infection of the genitourinary tract exists in a mild to severe degree. This occurs despite the routine use of antibiotics and the careful nursing care and supervision of the genitourinary complications. Why should a few of these patients, when all have genitourinary infection, die? Is it true that death is due directly to infection of the urinary tract, or are there other causative factors in the evolution of their disorder and complicating diseases which lead to the terminal state of uremia?

An analysis of the clinical histories of those patients who died, in most instances shows that they were subject to more than genitourinary infection. Many of them had had recurrent attacks of sepsis. Most of them had had several surgical procedures performed. Severe decubiti, osteomyelitis, heart lesions, pulmonary disease, gastrointestinal complications, general nutritional disturbances, etc., were encountered. It may be seen from the above cases that when the terminal picture was that of uremia due to kidney failure, in many of them other factors contributed to such an outcome.

The importance of this approach to the problem of the "cause of death" lies in the calling of attention to appropriate measures which are indicated in planning the best program of care for patients with injuries of the spinal cord. In addition to the use of antibiotics and to careful routine and repeated genitourinary studies, attention is called to the general bodily status of the patient, to his nutritional state, his reactions to surgical procedures, his organs of defense concerned with antibody and resistance elements, the spleen, reticulo-endothelial system, etc.

SUMMARY

A study was made of various important components of the bodily state in patients with injuries of the spinal cord.

The basal blood pressure was found to be low in cervical cord lesions. Orthostatic hypotension is noted, occurring most often in cervical cord lesions, and "black out" often results when the erect position is attempted. A reverse reflex hypertension, with headache and other unpleasant sensations, occurs during the administration of enemas.

Glucose tolerance curves are abnormal although there is no evidence of disease of the liver, pancreas, adrenal glands and thyroid.

There is a defect in concentration of the urine as well as in the day-night ratio, although no signs of kidney disease are noted.

There is stasis in the colon as determined by charcoal excretion tests. Gallbladder evacuation and concentration were normal.

Diarrhea was observed occasionally.

A constant finding in cord injuries was a great loss of weight which usually was not regained, and the mean of terminal weight loss was 31.5 pounds.

Hunger and thirst were experienced as well as a sensation of fullness after eating. Nausea was produced by various appropriate stimuli, as well as by retained feces and calculi. Hiccoughs were due to the usual causes. The water intake was greatly increased, particularly in cervical cord lesions.

An analysis was made of the causes of death and the pathologic findings in various organs, listed in order of frequency.

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In 1858, Brown-Séquard first distinctly expressed the opinion that "the nervous system determines an increase of the attraction exerted upon the blood by the living tissues, and, in this case, the phenomenon is attended by dilatation of blood-vessels. The nervous system acts directly and originally upon the parenchyma of the tissues." In 1860, Samuel, resting upon facts such as I have urged in regard to the vasomotor nerves, rejected them as the sole causes of nutritive changes, and declared his theory of trophic nerves as distinct fibres concerned in governing the nutritive condition of the tissues.

This observer conceived that the trophic nerves have their centres in the intervertebral spinal ganglia, or in cerebral ganglia having like physiological powers. He distinguished them as contripetal nerves, receiving and conveying inward impressions connected with trophic changes; and centrifugal nerves which, when palsied, give rise to atrophies, and, when irritated, to inflammations.

Thus, while he regards nutritive activity as the result of a force inherent in the molecules or cells of the tissues, he looks upon the trophic nerves as the means of regulating their changes, increasing, retarding, or enfeebling them, as the case may be.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequence*, published in 1872

Disorders of Electrolyte Metabolism in Diseases of the Central Nervous System

Irving S. Cooper, M.D.

In 1878, Claude Bernard[1] pointed out the importance of the "millieu interieur" in which the tissue elements live. This millieu interieur preserves the human organism from changes in its external environment by constantly preserving the conditions of life in its internal environment. Cannon[2] extended Bernard's theory of the constancy of the internal environment in his studies on the role of the autonomic nervous system in homeostatic mechanisms. The recent well-known studies of Selye,[3] dealing with the body's response to stress, have correlated and extended the postulates of Bernard and Cannon, and have precipitated considerable interest and widespread investigation into the mutual roles of the endocrine glands and the central nervous system in the response to stress and in certain neurometabolic syndromes of obscure origin.

The concept of control of metabolic functions by brain centers was indicated by Bernard in 1849 when he reported that puncture of the fourth ventricle of the brain resulted in glycosuria. Following Bernard, the studies of Harvey Cushing,[4] Ranson,[5] Magoun[6] and others led to the concept that the hypothalamus is the cerebral ganglion of the autonomic nervous system, and that the hypothalamus and its associated cerebral areas renders a vital effect on the endocrine glands and metabolism. The recent studies of Harris[7] regarding hypothalamico-hypophyseal relationships and Hume's[8] report of the role of the hypothalamus in the mechanism of triggering the alarm reaction have further heightened interest in this relationship.

These physiologic investigations have resulted in focusing clinical interest on certain neurometabolic syndromes, some of which have been recognized for many years, some described only recently. It is the purpose of this paper to bring to attention the occurrence of a syndrome of unusual and rarely recognized electrolyte disturbances associated with disease of the central nervous system, which appear to be secondary to the neurologic lesions. The electrolyte abnormalities with which this paper is particularly concerned are the

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development of marked retention of sodium and chloride in the plasma during the course of a disease involving the brain primarily. The unusual electrolyte disturbances in these cases can not be categorized in the present classifications of electrolyte disorders,[9,10] nor satisfactorily accounted for on the basis of our present knowledge of the control of electrolyte metabolism. Moreover, the blood levels of sodium and chloride recorded in these cases are among the highest ever recorded in the medical literature due to any cause.

REVIEW OF LITERATURE

The first report dealing specifically with hypernatremia and hyperchloremia associated with cerebral lesions, in the absence of renal disease, was that of Allott[11] in 1939. He presented five cases in which such electrolyte abnormalities were noted during the course of fatal disease of the brain. Allott's cases demonstrated hypernatremia, hyperchloremia and azotemia associated with a markedly decreased urinary excretion of sodium and chloride. Sweet and associates[12] reported hypernatremia, hyperchloremia, hyperglycemia, hypokalemia and gastrointestinal hemorrhages following a prefrontal lobotomy in a 47 year old woman who died on the thirty-second day after operation. Biemond[13] has described a syndrome of intermittent oliguria with edema of the face and hypernatremia secondary to a hypothalamic lesion in a 32 year old woman. Hypernatremia and hyperchloremia associated with cerebral lesions were reported in five cases of sulfonamide intoxication by Leutscher and Blackman.[14]

The author has, with MacCarty, previously reported three cases of hypernatremia, hyperchloremia and hypochloruria associated with cerebral lesions,[15] and has recently reported four additional cases with Crevier.[16]

Higgins et al.[17] have reported five patients with severe head injuries who developed moderately elevated levels of either sodium or chloride ions or both, and Peters[18] has mentioned a case of extreme sodium retention during the postoperative course of a patient following surgery for a craniopharyngioma. Prader[19] has also observed a marked hypernatremia in a seven year old boy with a craniopharyngioma.

The independent observation by several investigators of similar unusual electrolyte disturbances associated with neurologic disease, each of whom was impressed with the possibility that the marked retention of sodium and chloride might have been secondary to a cerebral lesion, indicates that this syndrome is of sufficient significance to warrant further investigation.

Table 1 summarizes the cases of this syndrome occurring in pathologically verified cases which have been reported to date. A brief survey of these cases reveals the fact that almost every one demonstrated frontal lobe or hypothalamic lesions, and that in each of these cases the values for serum sodium or plasma chlorides, or both, were far in excess of normal values and far higher than in previously described electrolyte disorders due to other causes.

Case 12 noted in table 1 was the first case of this syndrome which was studied by the author.[15] A 36 year old housewife presented symptoms of acro-

TABLE 1

SUMMARY OF 18 REPORTED CASES OF HYPERNATREMIA AND/OR HYPERCHLOREMIA ASSOCIATED WITH PATHOLOGICALLY CONFIRMED CASES OF INTRACRANIAL DISEASE

Author	*Pathologic Diagnosis*	*Highest Serum Sodium Recorded* (meq./liter) (Normal Value 135–145)	*Highest Plasma Chlorides Recorded* (meq./liter) (Normal Value 97–106)
Allott[11]	1. Ruptured aneurysm of anterior cerebral artery	153	120
	2. Cerebral infarct; frontal	162	108
Sweet et al.[12]	3. Prefrontal lobotomy	172	129
	4. Glioma of the third ventricle	—	129
Biemond[13]	5. Lesion(?) in region of tuber cinereum	155	—
Peters[18]	6. Craniopharyngioma	171	—
Higgins et al.[17]	7. Contusion involving base of frontal lobes	139	111
	8. Contusion involving base of frontal lobes	155	123
	9. Contusion involving base of frontal lobes	146	118
	10. Contusion involving base of frontal lobes	154	115
	11. Contusion involving base of frontal lobes	156	107
Cooper and MacCarty[15]	12. Pituitary adenoma and bilateral occlusion of anterior cerebral arteries	170	134
	13. Pitutiary adenoma	162	128
	14. Cerebrovascular accident left basal ganglia	161	129
Cooper and Crevier[16]	15. Cerebral maldevelopment	160	127
	16. Bilateral subdural hygroma	155	122
	17. Tumor in third ventricle of brain	169	132
	18. Craniopharyngioma	155	130

megaly and failing vision. Perimetric field examination demonstrated blindness in the right eye and a temporal defect in the left eye. Roentgenograms of the skull showed the sella turcica to be enlarged and eroded by an intrasellar tumor. On April 20, 1949, the intracapsular removal of a large pituitary tumor was carried out. During the operative procedure there was profuse arterial bleeding and both anterior cerebral arteries were ligated. The blood pressure remained within normal limits throughout the operation.

The patient responded well during the immediate postoperative period. However, from the third postoperative day she developed periods of stupor, muscular flaccidity and hypotension which lasted from one to 48 hours. During these periods the blood pressure fell as low as 40/0. Between these stuporous episodes the patient was mentally clear and on several occasions was able to walk unassisted. From the fourth postoperative day marked electrolyte abnormalities were observed. At this time the serum chlorides were 122.0 meq./liter, sodium was 170 meq./liter and potassium was 3.6 meq./liter. Hypernatremia and hyperchloremia persisted up to the time of death on the fortieth postoperative day.

Because of the unusual electrolyte findings in this case, the laboratory findings were reviewed in 3000 consecutive cases in which blood sodium levels

had been obtained, and nine cases were found in which the blood sodium had been elevated to 155 meq./liter or more. All of these cases were primarily neurologic problems. It was also particularly interesting to note that three of them had electrocardiographic tracings suggestive of hypopotassemia, although the serum potassium was not markedly depressed. Moreover, five patients demonstrated flaccid musculature of the type frequently seen in cases of hypopotassemia.[20] It is believed that the marked elevation of sodium in these cases results in potassium depletion by altering the sodium/potassium ratio.[21]

One of the cases reported by Cooper and Crevier is also worthy of mention.[16] This concerned a 56 year old colored woman who underwent craniotomy and subtotal removal of a craniopharyngioma on June 22, 1951. At the time of surgery, the neoplasm was seen to involve the optic chiasm, anterior cerebral arteries and floor of the third ventricle. The immediate postoperative course was uneventful, but during the ensuing five months she became progressively lethargic and died November 17, 1951. Blood and urine electrolyte studies were obtained throughout this period.

No electrolyte abnormalities were noted until two months postoperatively, at which time the plasma chlorides became elevated to 118 meq./liter. During the next two months, while the patient ate a regular hospital diet containing approximately 150 meq. of chlorides, the plasma chlorides varied from 103 to 130 meq./liter. The urine output varied from 600 to 1600 ml. in 24 hours, and contained from 10 to 59 meq. of chloride per liter. From October 26 through November 4 the patient received a salt-free diet. However, plasma chlorides remained elevated and varied from 112 to 125 meq./liter. Paradoxically, during this period of sodium chloride free diet, the urinary excretion of chlorides increased and varied from 47 meq./liter on October 29 to 122 meq./liter on November 1. No appreciable change was observed in the blood eyectrolytes when salt was again added to the diet during the last two weeks of life. Serum sodium varied from 139 to 155 meq./liter during the five months of observation.

During the last month of life there was a marked edema of the face and of the left extremities (figure 1). This remained localized to the right limbs and face until one week prior to death when the left limbs became slightly edematous. All four limbs became extremely flaccid and the deep tendon reflexes could not be obtained during the last two months of life. During this period the patient became progressively more drowsy and stuporous, and died on November 17, 1951.

DISCUSSION

The pathogenesis of the unusually marked elevation of serum sodium and plasma chlorides in these cases is not readily explained. Sufficient data are available in each of the cases reported to rule out hypertonicity of the blood due to dehydration. Moreover, there was no morphologic evidence of renal disease. It is unlikely that this marked hypernatremia and hyperchloremia

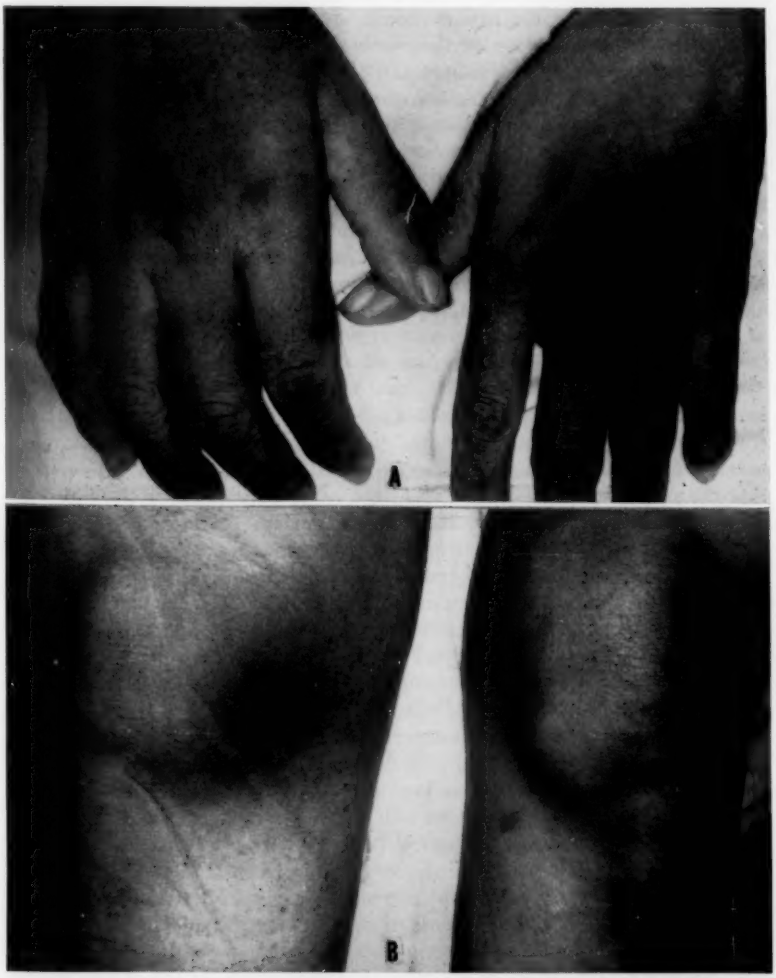

FIG. 1. *A.* Unilateral edema present in the case cited in text. *B.* Edema affecting the right upper extremities in same case. Note that the left extremities were uninvolved.

was due to an exaggerated alarm reaction or to adrenal hyperfunction. Allott postulated that varied intracranial lesions might in some way act through interference with the secretion of the antidiuretic hormone, thus producing excessive loss of water and causing retention of chlorides due to the absence of the chloruretic effect of this hormone.[11]

It is believed that the hypernatremia, hyperchloremia and hypochloruria in these cases is secondary to the cerebral lesions. The frequency of such markedly elevated levels of sodium and chloride in the blood associated with cerebral lesions seems to suggest a causal relationship between the cerebral lesions and the electrolyte abnormalities. This hypothesis receives considerable support from several physiologic investigations. Lewy and Gassman[22] reported the occurrence of elevated levels of chloride in the blood of cats following the production of lesions in the paroptic nucleus of the hypothalamus, and this nucleus has been demonstrated to be functionally related to the pars nervosa of the pituitary gland. Stevenson, Welt and Orloff[23] have recently reported that the experimental production of lesions in the ventromedian nuclei of the hypothalamus of rats resulted in an abnormal elevation of sodium in the serum. This increase is probably of a chronic nature, having been observed by them three to four months after placement of the lesions. These authors believe it is unlikely that the adrenal cortex plays a predominant role in causing the abnormalities shown by the hypothalamic animals.

The presence of an "osmo receptor" which responds to the effective osmotic pressure of the blood serum has been suggested by Verney.[24] He further states that the neurohypophysis responds to the osmotic pressure of the blood by regulating the secretion of antidiuretic hormone proportionately to changes in the concentration of osmotic components of the serum, 90 per cent of which consists of sodium salts. It is suggested that the high concentration in the blood of sodium and chloride in these cases is caused by interference with the sensitivity of, or damage to, the cerebral osmo receptor mechanism of Verney. It is worthy of note that the frontal lobes and/or hypothalamus were principally involved in 16 of 18 cases summarized in this report.

If these electrolyte abnormalities are, indeed, secondary to the cerebral lesions in these cases, one might expect to encounter occasionally an opposite clinical picture of sodium or chloride depletion associated with disease of the brain. Such a syndrome has, in fact, recently been described by Hilden.[25] Moreover, abnormal fall in serum sodium and plasma chlorides have been noted postoperatively in some cases of pituitary tumor.[26,27]

Further speculation is beyond the scope of this report. However, the physiologic implications of bizarre neurogenic electrolyte abnormalities are far-reaching and deserve further investigation. The practical implications of these bizarre electrolyte findings in cases of cerebral lesions are quite evident. The high mortality rate following neurosurgical procedures in the region of the third ventricle and hypothalamus have always been attributed to damage to "vital centers" located in the diencephalon. The precise cause for postoperative death in many cases, however, often remains obscure. In view of the fact that experimental hypertonicity of extracellular fluid, due to excess sodium and chlorides,[28] results in death from depression of the nervous system and respiratory failure, one wonders whether the extreme hypertonicity in such cases may not contribute to some deaths following intracranial surgery.

SUMMARY

A syndrome of marked hypernatremia and hyperchloremia associated with cerebral lesions has been discussed. The cerebral lesions associated with these disturbances usually involve the frontal lobes and/or hypothalamus. It is suggested that the clinical and experimental evidence at hand indicates these unusual electrolyte abnormalities to be secondary to the cerebral lesions. Accordingly, the markedly elevated serum sodium and plasma chlorides in these cases are considered to be neurogenic. The mechanism whereby cerebral lesions may cause retention of these electrolytes is not clear. However, it is suggested that damage to a cerebral osmo-receptor mechanism may be involved in the production of this syndrome.

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Neurologic Complications of the Hemorrhagic Diseases

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THE purpose of this paper is to group together the various hemorrhagic diseases and to review for the neurologist their clinical features and their nervous system complications.

Considerable progress has been made recently in diagnosing and in classifying these diseases. Quick in 1942[1] proposed the following classification, which is presented in a slightly condensed form:

I. Bleeding time prolonged; coagulation time normal.
  A. The purpuras
    1. With diminished platelets
      a. Essential thrombocytopenic purpura (Werlhof)
      b. Secondary thrombocytopenic purpura (infections, drugs, blood dyscrasias, toxins)
      c. Thrombotic thrombocytopenic purpura (Platelet thrombosis).
    2. With normal platelet count
      Senile and Schönlein-Henoch's purpuras.
  B. Hereditary pseudohemophilia
II. Coagulation time prolonged; bleeding time normal.
  A. Diminished prothrombin (hypoprothrombinemia)
    1. Due to lack of vitamin K. Hemorrhagic disease of the newborn.
    2. Due to toxins (Dicumarol).
    3. Idiopathic or familial hypoprothrombinemia.
  B. Diminished thromboplastin (Hemophilia)
  C. Diminished fibrinogen
  D. Anticoagulants (Heparin) liberated in anaphylactoid shock.

This classification will serve to introduce discussion of the individual diseases. It should be pointed out, however, that current developments in the field of hemostasis have led to a number of changes in the above groupings. Less emphasis is being placed on bleeding and clotting time determinations while more importance is now put on the prothrombin time and prothrombin consumption tests. Thus Quick[2] now suggests dividing many of these diseases

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into two classes, the hypoprothrombinemias and the hypoprothromboplastinemias. In the first class are the diseases with a prolonged prothrombin time, including vitamin K deficiency, poisoning from Dicumarol and allied drugs, and idiopathic hypoprothrombinemia. The second class, defined by a reduced prothrombin consumption, includes hemophilia, hemophilic-like disease and thrombocytopenic purpura.

ESSENTIAL THROMBOCYTOPENIC PURPURA

Essential or primary thrombocytopenic purpura (Werlhof's disease) is characterized by spontaneous, often recurrent, episodes of capillary bleeding into the skin, mucous membranes and other tissues. The platelet count is reduced, the bleeding time is prolonged, the cuff test is positive, and the clotting and prothrombin times are normal. An identical picture is produced in the secondary purpuras associated with infections, blood dyscrasias, drugs, etc., and only after these latter conditions are ruled out can a diagnosis of essential purpura be safely established. A group of cases remain, however, that fit into the general pattern described above. That this group is small is emphasized by the data from Perlman and Fox,[3] who from postmortem studies found only 1.7 per cent of cases of purpura to be of the idiopathic variety.

The disease may occur at any age, but it is most common between the ages of 12 and 45 years. Hemorrhages into the skin, from petechiae to massive eccymoses, are almost always present. They occur spontaneously or after slight bruising. Bleeding from the mucous membranes, especially from the nose and gums, are of equal importance. Bleeding may occur also in the kidney, bowel, bladder, nervous system and other tissues. The course is characterized by exacerbations and remissions extending over a period of years, though single episodes are not uncommon. All degrees of severity are known, from mild chronic cases to acute fulminating bleeding. Death may occur from exsanguination, or, more commonly, from bleeding within the nervous system. In childhood the onset often follows some infection, and the course tends to be mild with spontaneous recovery. Cases have been recorded in young infants and in infants with mothers suffering from purpura. Some investigators feel the disease is familial; others feel that perhaps it represents a group of similar diseases.

The pathologic changes in this disease are meager, aside from the evidences of and results from the bleeding. Proliferation of megakaryocytes with a decrease in platelet formation in the bone marrow has been described.[4] The pattern of bleeding within the nervous system varies from multiple capillary petechiae to large hemorrhages which destroy whole lobes of the brain. Since the essential pathologic involvement in purpura is bleeding at a capillary level, it is probable that small petechial hemorrhages are the basic lesions within the brain, and that larger hemorrhages have their origin from continued and confluent capillary bleeding. Subarachnoid and subdural hemorrhages occur as frequently as intracerebral bleeding, and in many cases hemorrhages are found both within the brain and in the meninges at the same time. The histo-

pathology of the lesions is one of pure hemorrhagic infiltration and destruction of brain tissue without much glial reaction. No specific vascular lesions are present, though endothelial cell swelling has been recorded.[5] Old areas of softening and gliosis are seen occasionally.

Although the incidence of bleeding within the nervous system is relatively rare in all the purpuras, it is a most serious complication and is the most frequent single cause of death. In a series of 75 cases published by Evans and Perry[6] there were 22 deaths, 12 due to nervous system hemorrhage. In 42 patients followed by Elliott[7] there were three deaths, one from an unrelated disease and two from cerebral hemorrhage.

Symptoms of nervous system involvement usually begin abruptly, with sudden collapse, coma and death. In some cases, however, the hemorrhagic manifestations develop gradually over a period of a few days or longer. In these cases the bleeding is most often within the brain substance. Symptoms indicative of focal brain destruction are somewhat more common than are those of meningeal hemorrhage. Such focal phenomena include weakness and hemiplegias, aphasias, sensory changes, visual field defects, reflex abnormalities and various disturbances of cerebration. The syndrome of subarachnoid hemorrhage with bleeding into the cerebrospinal fluid is also seen frequently. Convulsions, both focal and generalized in character, often accompany the headache and stiff neck. Fresh blood or xanthochromia is usually found in the spinal fluid.

Retinal hemorrhages are very common in purpura and are often seen without any obvious evidences of cerebral bleeding. Choked discs are occasionally seen and may be due to increased pressure or to bleeding within the optic nerves. Various ocular palsies and pupillary irregularities may occur with brain stem or other intracranial bleeding. Labyrinthine hemorrhage has been reported. Hemorrhages may also occur in other parts of the nervous system. Three cases of myelitis from bleeding within the spinal cord are recorded. Hemorrhages occasionally develop within peripheral nerves.[8]

When bleeding occurs in the nervous system, it usually begins during the latter stages of an acute episode or during the more severe exacerbations in chronic cases. It is most apt to develop when visceral bleeding is present. Although the prognosis is grave in any case of purpura with intracranial bleeding, it is not necessarily a fatal one. There are a number of reports of survival from both subarachnoid and intracerebral hemorrhage. In several of these cases the recovery dramatically followed splenectomy. This procedure should be instituted promptly, since once obvious brain destruction has occurred the results of splenectomy are disappointing as far as recovery of cerebral function is concerned.

OTHER TYPES OF PURPURA

The remaining types of purpura are the secondary thrombocytopenic purpuras, senile purpura, and Schönlein-Henoch's purpura. In the secondary purpuras—those caused by infections, blood dyscrasias, toxins and drugs—the in-

volvement of the nervous system is most apt to be associated with the primary disorder. Occasionally a picture of intracranial bleeding due to the purpura itself occurs. Garvey and Stephens[9] described a case of purpura due to sulfarsphenamine in which the patient died from a hemorrhage in the cerebellopontine angle. Ashworth and McKemie[10] reported two cases of cerebral purpura caused by salicylate poisoning.

Senile purpura is an ill-defined condition in which purpuric manifestations develop in older individuals without any apparent cause. The platelet count is usually normal, and the lesions are thought to be due to a capillary wall weakening as part of the aging process. Cerebral hemorrhages are occasionally reported as complications of purpura in this group.

Schönlein-Henoch's purpura is considered to be an anaphylactoid disorder in which purpura is but one of the manifestations of a generalized disease. Recurrent attacks of purpura may be associated with rheumatic symptoms (Schönlein) or with abdominal pains (Henoch). Other symptoms are fever, malaise, edema, urticaria and erythema. The platelet count is normal. A few cases are reported in which hemorrhages occurred in the nervous system in this syndrome. Symptoms which have been described include focal and generalized convulsions, hemiparesis, subarachnoid hemorrhage, intraocular bleeding and bleeding within the spinal cord.

THROMBOTIC THROMBOCYTIC PURPURA (Platelet thrombosis)

A group of cases has recently been described in which a purpura, an anemia and bizarre neurologic symptoms are the characteristic features of an acute febrile illness of fatal outcome. The first case of this syndrome was described by Moschcowitz[11] in 1925, and some 25 cases have now been recorded. Various names have been applied to this condition, including platelet thrombosis, thrombotic thrombocytopenic purpura, disseminated thrombocytic thrombosis, and thrombotic acroangiothrombosis. The etiology is unknown. Individuals of any age or sex may be affected. No cases have survived, perhaps because as yet the diagnosis rests on pathologic examination. In only one recorded case has an antemortem diagnosis been made.

The basic pathologic disturbance in these cases is a widespread deposition of hyaline thrombi in the arterioles, capillaries and venules. These thrombi are devoid of structure and have been considered by most investigators to be made up of masses of agglutinated platelets. The mechanism of thrombus formation is not known. Meacham et al.[12] suggest that the thrombus is the result of some degenerative process in the vessel wall. A moderate degree of endothelial proliferation may be seen in some vessels containing thrombi. Microinfarcts and petechial hemorrhages may be scattered throughout the tissues. In the brain the thrombi are found chiefly in the cortex and nuclear structures; few changes are seen in the white matter.[13] One may also find cellular hyperplasia of the small vessels, foci of nerve cell damage and petechial hemorrhages.[14]

The clinical features of the disease are exceedingly variable. The onset is usually preceded by vague prodromal complaints of malaise, aches and pains, nausea and vomiting and headaches for several days or weeks. The acute phase is marked by the appearance of purpuric symptoms, weakness, fever and neurologic and mental symptoms. A profound anemia is usually noted, with hemoglobin values ranging as low as 20 per cent. The platelet count is reduced, the bleeding time prolonged, the cuff test positive and the clotting time normal. The course of the disease is one of an intermittent but progressive increase in severity of symptoms. Death occurs in from two to four weeks, though shorter and longer survival times have been recorded.

The prominence of the neuropsychiatric symptoms is striking.[15,16] Clough[17] states, "The most distinctive clinical feature is the appearance, usually late in the disease, of bizarre fluctuating neurologic disturbances of almost any conceivable type." Mental symptoms predominate. Restlessness, irritability, drowsiness and confusion gradually progress to delirium, dementia, stupor and coma. Once consciousness is lost death follows in a few days. Almost any focal symptoms may occur. Motor paralysis was found in seven of 14 cases reviewed by Adams et al.[14] Generalized seizures occurred in three cases. Other findings included hemianesthesia, aphasias, and flaccid paraplegia. In a case described by Singer, Bornstein and Wile[18] an 11 year old girl became incoherent, complained of dizziness and had paresthesias in all extremities on the third day of illness. These disappeared after a few hours. Two days later she became very restless and complained of a severe frontal headache. Later she became confused and expired in coma the next day. Muirhead et al.[19] described the case of a 14 year old girl whose first symptom was a transient paralysis of the left arm two weeks before admission. This recurred a week later and again on the day of hospitalization, this time accompanied by jerking movements of the arm. The patient then developed purpura, fever, nausea and vomiting, and anemia. Before death eight days later she experienced fluctuating paresthesias of the face and trunk, weakness of the right arm and irrational interludes. Terminally there was a marked mental deterioration with coprophagia and extreme dementia.

No treatment has proved useful. Splenectomy has been performed in a few cases but only when the patient was already gravely ill. Multiple transfusions and other supportive therapy has not stopped the fatal progress.

HEREDITARY PSEUDOHEMOPHILIA

Hereditary pseudohemophilia (hereditary hemorrhagic diathesis, thrombasthenic purpura) is a hemorrhagic disorder characterized by a prolonged bleeding time; the coagulation time, blood platelet count, and clot retraction are normal. The symptomatology is chiefly one of excessive and prolonged bleeding, either spontaneously or after slight trauma or operations. Petechial bleeding is rare. The condition is often familial and may develop at any age. The bleeding tendency lasts for many years, though it usually diminishes in sever-

ity as the patient grows older. It rarely causes death. It is distinguished from hemophilia by the prolonged bleeding time and normal coagulation time. These are reversed in hemophilia, and this latter disease does not occur in females though pseudohemophilia does. According to Estren, Medal and Dameshek,[20] who have recently reviewed 62 known cases of this disease, the pathologic disorder is due to some inherent defect in the ability of the capillaries to retract following trauma. No specific treatment is known, and therapy consists largely of prophylactic measures. The best way to stop the bleeding is by pressure or by the use of thrombin-fibrin foam.

Bleeding into the nervous system is rare but occasionally occurs. Retinal hemorrhages with blindness has occurred in a number of families. Other complications include subdural and intracerebral hemorrhage.

HEMORRHAGIC DISEASE OF THE NEWBORN

Hemorrhagic disease of the newborn (Morbus hæmorrhagica neonatorum) has been recognized as a clinical entity for many years. It is characterized by a spontaneous and self-limiting bleeding tendency in the first week of life. In recent years, it has been found that the bleeding is associated with a low prothrombin level which in turn is due to a lack of vitamin K. The disease occurs in about half of one per cent of all newborn babies. Bleeding usually begins after the second day of life and reaches its height by the fourth day. Only occasionally is the onset as late as the second and third weeks. The bleeding is usually a slow oozing which may originate from the umbilical stump or from the intestinal tract (melena neonatorum), or which may appear as ecchymoses into the skin, and elsewhere. It is often precipitated by slight trauma. The prothrombin level is low and the clotting time is prolonged. Treatment consists of replacing the blood loss and of the prophylactic and therapeutic administration of vitamin K.

The most serious complication is intracranial hemorrhage, and this is the most common cause of death. According to Clifford,[21] intracranial bleeding develops in from 10 to 20 per cent of all cases.

The pathologic changes are those of multiple hemorrhages in the dura, leptomeninges and brain. Similar changes are seen in bleeding due to birth trauma and it is impossible to separate the two conditions pathologically. Actually the bleeding due to hypoprothrombinemia may start from small vessels damaged during the birth process.[22] Ferraro and Roizin[23] found that central nervous system hemorrhages in rats fed a deficient vitamin K diet were definitely precipitated by trauma.

The symptoms of cerebral bleeding in hemorrhagic disease of the newborn are identical with those of cerebral birth injury, except that in the former they are associated with hemorrhages elsewhere in the body. The infant has a feeble cry, becomes somnolent and stuporous, feeds poorly and develops vomiting. Convulsions are common, and there may be various states of spasticity and rigidity. Cyanosis is present, the fontanelles often bulge, and there is blood in the spinal fluid. The mortality rate is over 50 per cent in these cases.

The relationship of intracranial hemorrhage in the newborn to hemorrhagic disease is still not clear. After the introduction of prophylactic vitamin K therapy to mothers and babies in 1939 there were many reports stating that hemorrhagic disease of the newborn and spontaneous intracranial hemorrhage would soon be a thing of the past. Other reports were contradictory. Sanford et al.[24] found the incidence of all hemorrhagic manifestations, including cerebral hemorrhage, to be the same in two series of cases, one with and one without vitamin K. Potter[25] presented a convincing study of two large groups of cases investigated over a period of four years. For the first two years mothers were given vitamin K and for the following two years they were not. There were over 6,500 cases in each group. The incidence of intracranial hemorrhage, total mortality rates, and other comparisons were the same in the two groups.

The occurrence of retinal hemorrhages in the newborn has also been ascribed as being due to a low prothrombin level.[26] In a later study by Falls and Jurow[27] it was found that retinal hemorrhages appeared in 32 per cent of babies whether or not vitamin K was given to the mothers, and there was no correlation between hemorrhages and a low prothrombin level.

It is apparent that there is still a great deal to be learned about hemorrhagic disease of the newborn and the intracranial bleeding associated with it. There can be no doubt that it exists as a disease syndrome and that intracranial bleeding is one of its most severe complications. However, restoring the prothrombin level to normal by administration of vitamin K to the mother or to the infant has not solved the problem of hemorrhagic disease of the newborn if the recent statistical studies are valid. The apparent peak incidence of intracranial bleeding in the winter and spring months, according to Waddell[28] and Kerpel-Fronius,[29] also needs further study and clarification. One might speculate that there is some other factor, possibly dietary, which is associated more directly with the bleeding tendency and that the hypoprothrombinemia which is restored to normal by vitamin K is a related but more incidental phenomena.[30]

BLEEDING FROM HEPARIN AND DICUMAROL

Heparin is an anticoagulant which is found normally in various organs and tissues of the body, particularly the lungs and liver. Because of its effect in inhibiting coagulation of the blood it has been used clinically in the prevention and treatment of thromboembolic disease. It must be given parenterally and its effect is lost rapidly. For this reason the patients receiving it are hospitalized; any bleeding from an overdosage is quickly seen, and is quickly controlled by immediately stopping the treatment. Complications due to bleeding are therefore rare.

There have been several cases of subacute bacterial endocarditis in which cerebral hemorrhages appeared to occur more frequently with heparin added to the therapeutic program. This has also been noted with dicumarol and it is generally agreed that both heparin and dicumarol are contraindicated in

bacterial endocarditis.

Dicumarol is the active principle isolated from spoiled sweet clover, the ingestion of which causes a hemorrhagic disease in cattle. It causes a hypoprothrombinemia which is relatively refractive to vitamin K. As in heparin there is a danger of hemorrhage if the prothrombin time is allowed to get too low from over-dosage. This is quite easy with dicumarol since it is taken orally, and proper supervision may be lacking in making sure the prothrombin time does not fall to too low a level. Cosgriff et al.[31] state that 20 to 25 per cent of persons who receive dicumarol are hyper-reactors to the drug, in that the conventional dosage produces a prolongation of the prothrombin time to levels at which hemorrhage may occur. They state that bleeding occurs in 6 per cent of cases and is of major importance in 1 to 2 per cent.

Duff and Shull[32] have recently summarized the fatal cases of bleeding from dicumarol. They surveyed 24 cases in which death was attributed to the anticoagulant therapy. Of these, seven were in patients suffering from subacute bacterial endocarditis, in six of which the hemorrhages were in the brain. In five other cases the fatal hemorrhage was cerebral in location.

Sydow[33] described a case of cerebral bleeding in an infant born to a mother who was given dicumarol for a month prior to delivery for a thrombosis complicating pregnancy. Though the mother maintained an adequate prothrombin level, the level in the infant was less than 10 per cent at birth. It remained low for six days despite repeated doses of vitamin K.

IDIOPATHIC (FAMILIAL) HYPOPROTHROMBINEMIA

In this group are included those cases of abnormal bleeding in which there is a permanent lack of normal amounts of prothrombin in the blood. Clinically the disease resembles hemophilia. Bleeding occurs from the nose and gums, from the gastrointestinal tract, kidneys and uterus, and into the subcutaneous tissues. Hemarthroses are common. The clotting time is usually prolonged and the bleeding time normal. The prothrombin time is always prolonged in contrast to hemophilia in which the prothrombin time is normal. The platelet count is normal and the cuff test usually negative. A familial tendency has been found in about half the reported cases. Though the bleeding is associated with a low prothrombin concentration, there is no response to the administration of vitamin K. Repeated injections of plasma may control the bleeding.

In the first case of this syndrome reported, death was due to bleeding within the brain.[34] The patient first developed bleeding at the age of nine months. During his twenty-third hospitalization at the age of 17 he developed an adductor palsy with sensory changes referable to the second, third and fourth lumbar nerve roots on the left. This was associated with a hemarthrosis of the left hip. During the twenty-sixth admission at the age of 18 the patient complained of headache, had a stiff neck, became stuporous and died a short time later. Postmortem examination revealed an organizing subdural hematoma, and a recent hemorrhage near the left basal ganglia.

HEMOPHILIA

Hemophilia is an hereditary disease in which abnormal bleeding occurs as a result of delayed coagulation of the blood. The original definition by Otto in 1803 stating, "Males only are affected and all are not liable to it. Though females are free, they are capable of transmitting it to their children," (Quick[1]) is difficult to improve.

The cause for the prolonged coagulation time in hemophilia is thought to be due to a lack of available thromboplastin, which is necessary for the conversion of prothrombin to thrombin. Both platelets and plasma are necessary in the proper production of thromboplastin, and recent work indicates that a plasma factor, thromboplastinogen, is deficient in these individuals.[35]

The only constant abnormality in the blood is a prolonged coagulation time. The bleeding time is usually normal, as are the prothrombin time, cuff test and platelet count. The hemoglobin and red blood cells are normal, or reduced if considerable bleeding has recently occurred.

The clinical picture in hemophilia is characterized by prolonged bleeding either spontaneously or after slight trauma from various parts of the body. The bleeding is not of the purpuric or oozing type but is usually massive into the subcutaneous tissues, muscles, joints, and visceral cavities. The clot which forms is soft and friable and bleeding continues around it, sometimes for days and weeks. The most striking site of bleeding is into the joints, especially those subject to trauma and weight bearing. Subcutaneous and intramuscular bleeding are present in every case at one time or another, and the patient may have epistaxis, bleeding from the gums following extraction of teeth, bleeding from the tongue if it is accidentally bitten, hematuria, bleeding into the gastrointestinal tract, and elsewhere.

The disease usually begins during the first or second year of life, and rarely starts after the fourth year. The course is erratic, with episodes of bleeding occurring at any time, but most often following some slight trauma. About three-fourths of the patients die before the age of 20. Treatment consists of the avoidance of trauma if possible, and multiple transfusions of blood and plasma to control bleeding episodes.

Bleeding within the nervous system is relatively rare in hemophilia, as contrasted to its incidence in the purpuras. In a series of 267 cases of hemophilia collected by Birch[36] there were 19, or about 7 per cent, with bleeding into the nervous system. A similar incidence was reported by Skold[37] in Sweden, in which cerebral hemorrhage occurred in five of 72 cases.

The site of nervous system hemorrhage may be intracerebral, in the meninges, in and around the spinal cord, or involving the peripheral nerves. Intracranial hemorrhages are most often spontaneous, while bleeding into the spinal canal or cord often follows some trauma to the back. Bleeding within the cranial cavity is usually fatal, though there are a few reports of subarachnoid and intracerebral hemorrhage with subsequent recovery. Hemorrhages into the spinal canal are much less serious and recovery may follow even

severe paralysis. It is recommended that surgical exploration be undertaken for removal of a possible hematoma.

The peripheral nerve involvement is usually caused by compression from hemorrhages within the muscles or fascial planes in which the nerves are located. Almost any nerve may be affected, and reports include the facial, median, ulnar, radial, femoral, sciatic and peroneal nerves. The symptoms may be either of partial or complete interruption of function, and recovery is common. The most frequent nerve which is affected is the femoral nerve, following hemorrhages into the iliopsoas muscle. Severe involvement leads to atrophy of the thigh and difficulty in walking. Next in frequency of involvement is the ulnar nerve, due to its proximity to the elbow joint. Lesions of this nerve are confused with Volkmann's ischemic contracture of the hand following hemorrhage into the muscles of the forearm.

AFIBRINOGENEMIA

In this condition abnormal bleeding is due to a congenital absence of fibrinogen in the blood. It is very rare. Clinically the disease most closely resembles hemophilia, since prolonged bleeding has often followed slight cuts or trauma. On testing the blood, however, it is found that no clot forms no matter how long it stands. No fibrinogen can be detected in the blood. A clot will form if fibrinogen is added, and transfusion will cause clotting for a time by supplying the lacking fibrinogen. The disease is not as severe as hemophilia, and there are long periods when no bleeding occurs.

In one of the six cases known, that reported by Schonholzer,[38] a 15 year old boy died from a cerebral hemorrhage. He had experienced episodes of bleeding from birth, and the brain hemorrhage occurred spontaneously. Postmortem examination revealed a giant dural hematoma over the right frontal lobe, and a large extravasation of liquid blood in the right hemisphere.

SUMMARY

The neurologic complications of the hemorrhagic diseases are in general those due to hemorrhage within or around nervous tissue. Intracranial bleeding is infrequent in these diseases but is of most serious consequence.

The condition described as thrombotic thrombocytopenic purpura or as platelet thrombosis is relatively rare but of considerable neurologic interest, since almost all of some 25 reported cases had marked symptomatic and pathologic involvement of the nervous system.

Hemorrhagic disease of the newborn is presumably due to a deficiency in vitamin K. The early promise of a reduction in the incidence of cerebral hemorrhage in infants supplied with vitamin K has not been fulfilled, and the problem awaits further investigation. The uncontrolled use of heparin and dicumarol may result in bleeding in the brain and elsewhere.

Bleeding within the nervous system in hemophilia occurs in about seven per cent of the cases. The most frequent lesions are peripheral nerve compressions by a neighboring hematoma.

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Spinal Fluid Findings Following Cerebral Angiography

Joseph M. Stein, M.D. and Max Fink, M.D.

With increasing use of cerebral angiography, the problem arose as to whether the procedure, of itself, produced changes in the cerebrospinal fluid. Forty-eight hours after angiography a spinal fluid examination in a patient suspected of a brain tumor revealed a cloudy fluid with 3,000 white blood cells per cu. mm. Prior to angiography the fluid had been clear, colorless and without any cells. As no information concerning the relationship of pleocytosis to angiography was available, it was decided to study the changes in the spinal fluid by the usual clinical methods.

Spinal fluids from 21 patients were examined prior to and following angiography. Lumbar punctures prior to angiography were done at various intervals, but all punctures following angiography were performed between 12 and 24 hours after the procedure. In each instance the spinal fluid was examined for color, cell count and total protein content.

All angiograms were percutaneous, using 35 per cent Diodrast as the contrast medium. Maximal Diodrast volume was 70 ml. at one procedure. While the majority of patients were subjected to unilateral carotid punctures, bilateral punctures were done in four, and combined bilateral carotid and vertebral punctures in one patient. Either intravenous Pentothal (14 cases) or local procaine (seven cases) anesthesia was used.

RESULTS

Of the 21 subjects, significant changes in the spinal fluid following angiography were seen in only two cases. In one, a patient with a cerebral angiomatous malformation and multiple aneurysms, 5,000 red blood cells per cu. mm. were seen in a pink spinal fluid. In the second, a patient with a chromophobe adenoma of the pituitary gland, the protein content of the spinal fluid changed from 89 to 151 mg. per cent; also, seven lymphocytes per cu. mm. were recorded when previously there had been none.

In all other subjects, changes in color, protein content and cell count were not significant. Three subjects showed transient hemiparesis following an-

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giography, and in none of these were there significant changes in the spinal fluid. Since Diodrast can cause changes in membrane permeability,[1] and the spinal fluid reflects such changes, it could be postulated that a relationship between complications following angiography and changes in the spinal fluid might exist. Such changes were not demonstrated in the present cases. Further investigations with more exacting techniques for protein determination and protein differentiation are indicated.

CONCLUSIONS

Neither a marked pleocytosis nor a marked increase in protein content of the spinal fluid are usual concomitants of Diodrast angiography. It may be concluded that when such spinal fluid changes are found they are unrelated to the procedure.

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The causes of encephalitis are mechanical injuries of the head itself—blows, falls, contrecoups; excessive mental application, anxiety, &c.; the intemperate use of spirits; exposure to the sun-beams; &c. Frequently, encephalitis forms a complication of other diseases of the system, or of distant organs, especially fevers, the exanthemata, and dropsies. It is also frequently the *effect* of other diseases of the encephalon itself; it is excited round the coagulum, or cyst, in cases of cerebral haemorrhagy,—tumors, tubercles, &c.; it is also sometimes excited by ossifications, or projection spiculae of bone. Meningitis and myelitis frequently excite each other. M. Lallemand details a case in which a ligature applied to a part of the *right* brachial plexus induced inflammation and suppuration of the posterior part of the *left* hemisphere of the brain (De l'Encéphale, t. i., 122, 226).

Encephalitis is said to have followed the suppression of the catamenia and other discharges. Is it ever connected with rheumatism?

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

PEDIATRIC NEUROLOGY

This new department has been instituted to give more specific attention to the many neurologic diseases and conditions occurring among children.

DOUGLAS N. BUCHANAN, M.D.
Section Editor

Neurologic Lesions in Relation to the Sequelae of Birth Injury

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IN ORDER to examine whether certain factors during labor or at birth predispose to neurologic lesions, we have made a statistical study of certain groups of infants who were born in a local hospital in Rochester, Minnesota. These groups are classified as (1) those in whom neurologic abnormalities were present in the neonatal period, (2) those born after prolonged labor, or exhibiting asphyxia or delayed respirations at birth, (3) those whose births were associated with abnormal placentas or cords, and (4) those born of mothers having toxemia or hypertension, or both, during pregnancy. The records of 4,464 infants and their 4,411 mothers, for the period January 1, 1944 through December 31, 1947 were reviewed and the above groups were selected. Many of these infants have been followed for periods varying from one to seven years (the average period of observation was five years) by repeated examinations by our pediatricians or by letter to the parents.

LITERATURE

Little[1] in 1862 was the first to give a clear description of the condition he called "spastic rigidity" and which has become known as "Little's disease." He attributed the condition almost wholly to asphyxia of the nervous system of the infant occurring as the result of accident or other injurious process during birth. Of 63 cases reported in Little's paper, postmortem findings are described in only two. In one case there was evidence of old intracranial hemorrhage and in the other, a stillborn infant, effusion of blood and congestion of all the blood vessels were noted. McNutt (1885)[2] discurred in ten babies, suggesting that meningeal hemorrhage was the cause of

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the sequelae in those that recovered. Freud (1897)[3] was unable to find evidence that "cerebral diplegia" was due to birth injury. Collier (1899,[4] 1924)[5] concluded that diplegia was due to neuronic degeneration and not to meningeal or other hemorrhage.

It is controversial whether cerebral asphyxia or lack of oxygen alone can cause permanent changes in brain tissue with resulting neurologic manifestations in childhood. Hannes (1911)[6] reported a study of three groups, each composed of 150 children. The groups were made up as follows: (1) those who had had asphyxia, (2) those who had been subjected to version or breech extraction or both, and (3) those who had been born by normal spontaneous delivery. In each group there was an equal number of apparently abnormal, backward, and defective children. Ford[7] could discover no evidence that permanent injury might be produced by asphyxia due to oxygen deprivation. McPhail and Hall (1941)[8] found that a group of children who had been apneic at birth did not show evidence of mental retardation when they reached school age. Campbell and his associates[9] could find no evidence of mental or physical retardation after eight to 11 years among a group of infants with severe delay in establishing normal respiration at birth.

Several workers, however, have stated that neurologic disorders can result from "anoxic" damage to the nervous system (Schreiber,[10] Lund,[11] Courville and Marsh).[12] Darke[13] studied the mental status of children who had been severely asphyxiated at birth. On examination of his results as reported, the difference in mental status, which appears statistically significant, does not seem individually important in most of his cases. Windle's[14] work with animals demonstrated that complete asphyxia during birth could produce severe changes in the central nervous system and could cause neurologic symptoms immediately after birth, alhtough the symptoms frequently were only transient.

Few studies have determined whether toxemia of pregnancy, and placental or cord changes have any effect on infants and particularly on those surviving the neonatal period. It is well known that the stillbirth and neonatal death rates are higher among infants of these groups than among control groups. Brash[15] has shown that infants of toxemic mothers who survive the neonatal period are not liable to permanent changes.

NEUROLOGIC LESIONS

In 1950 two of us (Keith and Norval)[16] reported the incidence of neurologic lesions among 4,464 babies born from 1944 through 1947.

Fifty-seven of the infants (1.3 per cent) included in the previous study had clinical or pathologic lesions that affected the nervous system primarily and that were evident during the first two weeks of life. Among these were seven stillborn infants, of whom five were anencephalic; the sixth infant had spina bifida and meningocele; the seventh was delivered by breech extraction, and necropsy showed no evidence of hemorrhage or other injury.

Eighteen babies died during the first week of life and 10 others died during the first eight months of life. Six of the 18 babies had demonstrable intracranial hemorrhage, of whom five were delivered spontaneously without difficulty and one was born by breech extraction, but the delivery was not considered difficult. It would seem that the so-called difficulties of delivery had little to do with the occurrence of intracranial hemorrhage, although the lesions which were demonstrated were definitely traumatic. Among the remaining 22 infants, all had gross lesions and in 20 of them the clinical

and pathologic findings were such as to preclude injury or difficulty in delivery as causes of death; the remaining two babies quite probably suffered from birth injury. One had a subdural hydroma which was evacuated surgically, but the child survived for only 10 weeks. His was a "difficult delivery" and this undoubtedly contributed to or was responsible for his death; however, he had a congenital anomaly of the retina, and at operation the brain was seen to be small and shrunken, suggesting other congenital anomalies. The other injured baby had an intraventricular hemorhrage. A communicating hydrocephalus was demonstrated at 12 weeks of age by means of dye injection and at necropsy. This suggests that the hydrocephalus was present at birth and that the hemorrhage was the result of trauma but not the cause of the hydrocephalus.

Twenty-two of the babies remained alive for more than eight months. Two were microcephalic, six had mongolism and five had gross structural abnormalities of the central nervous system. Follow-up studies on the remaining nine babies gave useful information. One of these had multiple congenital abnormalities and convulsions, and died at two and a half years of age. Six babies had convulsions or twitching in the neonatal period, but were normal when observed at ages ranging from seven months to four and a half years. The remaining two were born after difficult deliveries. In one, asphyxia was present, respiration was delayed for 12 minutes and bilateral brachial palsy was observed. No special treatment was carried out, the palsy disappeared in two months and the child remained quite well for a year following. In the other case of difficult delivery the help of low forceps was required; the baby had two convulsions a few hours after birth but had no other difficulties and remained well at 15 months of age.

The foregoing paragraphs may be summarized as follows: Among 57 infants with neurologic lesions there were only five with frankly difficult births. Two recovered completely, one died of a subdural hematoma, one of hydrocephalus and intraventricular hemorrhage, and one after attacks of cyanosis. Delivery in this last case was a "difficult breech" and necropsy showed evidence of anoxia but no hemorrhage. It seems reasonable to conclude that in this group of infants, difficulties during delivery had comparatively little to do with persistent neurologic abnormalities in most of those who survived.

ROLE OF PROLONGED LABOR, ASPHYXIA OR DELAYED RESPIRATION

Previously we reported the incidence and role of prolonged labor, asphyxia or delayed respiration among 2,306 babies born to 2,281 mothers during the period January 1, 1944 through June 30, 1946. The present study is an extension of the previous one, for we reviewed the records of 4,464 infants born to 4,411 mothers from January 1, 1944 through December 31, 1947.

The grouping of cases according to certain factors which involved labor and delivery was as follows:

Group 1. Prolonged first stage of labor (more than 1,000 minutes or sixteen and one half hours). Prolonged second stage of labor (primipara, more than 120 minutes; multipara, more than sixty minutes). Both first and second stages prolonged.

Group 2. Controls for group 1.

Group 3. Asphyxia livida or pallida. Delayed respiration (beyond one minute).

Group 4. Controls for group 3.

Group 1. *Prolonged Labor.* Of the 4,411 mothers, 397 had prolonged labor. To these 397 mothers, 402 infants were born. During the neonatal period, 370 babies (92 per cent) were considered

normal and 32 (8 per cent) were abnormal. (In the previous study[16] corresponding figures were 91.2 per cent and 8.8 per cent.) Three of the abnormal infants were stillborn and 11 died; death could be attributed to birth injury in five of them. Three of these 14 had intracranial hemorrhage, the result of birth injury. One died in asphyxia pallida, but no hemorrhage was present. One died of intra-uterine asphyxia and one of "cerebral anoxia"; in neither case was intracranial hemorrhage found. Three infants died of prematurity. Two other infants had a gross neurologic abnormality (spina bifida and meningocele) and died. One died following repair of an esophagotracheal fistula. A diabetic mother delivered one of the stillborn infants. The cause of stillbirth of the fourteenth infant was not noted.

Of the remaining 18 abnormal infants, nine had cyanotic spells; two, twitching of the muscles; one, palsy of the right lower lip; one, erythroblastosis; one, fever; one, fractured clavicle; one, fractured skull; one, swelling of the thigh; and one, laceration of an eyelid.

Group 2. *Controls for Group 1.* From the total group of 4,411 mothers, 397 who had had relatively short uncomplicated labor were arbitrarily chosen as controls. To these 397 mothers 397 infants were born. Three hundred and eighty-two (96.2 per cent) were considered normal and 15 (3.8 per cent) were abnormal. In this group, four infants were stillborn and three died. One of the seven (14.3 per cent) died of birth injury with intracranial hemorrhage, one of congenital heart disease, and one of multiple congenital anomalies. Of the stillborn, one had anencephaly and one had hydrocephalus; in the other two the cause of stillbirth was not stated.

Of the remaining eight abnormal infants one had spina bifida occulta; one, paralysis of the left lower lip; one, twitching of muscles; one, erythroblastosis; one, cyanosis; two, congenital heart disease; and one, fever on the third day of life.

From these figures it appears that the number of stillbirths and neonatal deaths was greater in the group in which labor was prolonged than in the controls (3.5 per cent and 1.7 per cent respectively). As might also be expected cerebral injury with hemorrhage and death occurred more often in the group in which labor was prolonged than in the controls (15.6 per cent and 6.6 per cent respectively). Prolonged labor approximately doubled the risk of stillbirth or neonatal death and of fatal intracranial hemorrhage.

Follow-up Studies of Group 1. (Prolonged Labor.) It was possible to follow 349 of the 402 infants in this group (14 died and 39 were lost to follow-up investigation). They were observed over periods varying from one to seven years. Eighteen of the 32 abnormal infants in this group survived the neonatal period. No follow-up information is available in two cases, and the one child who had erythroblastosis was followed for only five months, at which time he appeared quite well. The remaining 15 children were observed for periods varying from one to seven years, and all 15 were considered to be normal healthy children. No psychometric tests were done on these children, nor have they entered school as yet.

Thirteen of the 370 presumably normal infants in this group had neurologic signs or symptoms after the neonatal period. Of these, eight had convulsions associated with fever, but appeared normal otherwise at two to five years of age. One had torticollis but was normal at three years of age. One was found to be mentally retarded at three years of age. One child developed strabismus which remained fixed and one died sud-

TABLE 1

INFANTS HAVING ASPHYXIA OR DELAYED RESPIRATION, WITH CONTROLS: NEONATAL PERIOD

	Asphyxia or delayed respiration		*No asphyxia*	
	No.	*Per cent*	*No.*	*Per cent*
Normal infants	181	76.7	225	95.3
Abnormal infants	55	23.3	11	4.7
Died	34		6	
Cyanotic	7		1	
Mongolism	1		1	
Brachial palsy	1			
Spina bifida	1			
Depressed skull fracture	1			
Fractured clavicle	1			
Swelling, thigh	1			
Erythroblastosis	1		1	
Asphyxia pallida	1			
Cleft palate	1			
"Poor cry"	1			
Laryngeal stridor	1			
Twitching, jerking	2			
Subdural hydroma (died 6 wk.)	1			
Congenital heart (died 6 wk.)			1	
Fever			1	
Total	236	100.0	236	100.0

denly at 13 months of age (Waterhouse-Friderichsen syndrome). One had an attack of "disorientation" but was normal at four years of age.

Follow-up Studies of Group 2. (Controls). It was possible to follow 328 of the 382 infants in this group (eight died and 61 were lost to follow-up investigation) for periods varying from one to seven years. Eight of the abnormal infants in this group survived the neonatal period. One child has not been observed. One infant with congenital heart disease died at the age of nine months. One had spina bifida that was not noted at birth. The remaining five children appear to be developing normally at three to five years of age.

Seventeen of the 382 presumably normal children in this group had neurologic signs or symptoms after the neonatal period. Ten had convulsions associated with fever but eight of them appeared normal at ages varying from two to seven years (two were not observed). Two children had a convulsive disorder, one dying in a convulsion at the age of one year, and the other having convulsions at five years of age. Three children had strabismus. Another was mentally retarded, and the seventeenth had spina bifida occulta.

Group 3. Asphyxia or Delayed Respiration Present. There were 236 babies in this category; 181 (76.7 per cent) of these were normal and 55 (23.3 per cent) were abnormal in the neonatal period. Thirty-four of the 55 abnormal babies died in the neonatal period. The remaining 21 babies had various abnormalities as noted in table 1.

One may study the influence of birth weight among these infants who had asphyxia or delayed respiration at birth. Those infants who had birth weights of less than 2,500 gm. are considered premature. There were 46 such infants. Twenty-two of them were considered normal in the neonatal period and 24 abnormal. Twenty-two of the 46 died and follow-up studies were made on 23 (one was not traced). Twenty-one of

TABLE 2

PREMATURE INFANTS WITH ASPHYXIA OR DELAYED RESPIRATION

Respiratory delay, minutes	*Neonatal period*				*One to seven years after birth*			
	Normal	*Abnormal*	*Died*	*Total*	*Normal*	*Abnormal*	*Total*	*Not followed*
None	5	1	8	14	6	0	6	8
1 - 5	9	1	7	17	7	2	9	8
6 - 10	5	0	1	6	5	0	5	1
11 - 15	0	0	1	1	0	0	0	1
16 or more	1	0	2	3	1	0	1	2
Not stated	2	0	3	5	2	0	2	3
Total	22	2	22	46	21	2	23	23
Per cent	47.8	4.3	47.8	100	91.3	8.7	100	

the 23 were normal at ages varying from one to seven years, one had strabismus, and one was suspected of having "cerebral palsy" at four months but was quite normal at five years of age (table 2). It seems evident that asphyxia and delayed respiration in premature infants did not cause neurologic disturbance in those who survived.

The remaining 190 infants weighed 2,500 gm. or more at birth. Thirteen of these died, 158 were normal and 19 were abnormal in the neonatal period. It was possible to follow 160 of these children for periods ranging from one to seven years (table 3). Six of them were found to have abnormalities. One had mongolism (not diagnosed at birth), one strabismus and mental retardation, one strabismus alone, one asymmetry of the sternocleidomastoid muscles, one a convulsion with fever, and one was suspected of having "cerebral palsy" but was normal at two and a half years of age.

Group 4. Controls for Group 3. A group of 236 babies who did not have asphyxia or delayed respiration was arbitrarily chosen as controls for the group of babies who did have these conditions. Two hundred and twenty-five (95.3 per cent) of those infants were normal in the neonatal period and 11 (4.7 per cent) were abnormal. Six of these latter died, the remaining five having abnormalities as noted in table 1.

Follow-up Studies of Groups 3 and 4. In group 3 (those with asphyxia) it was possible to make follow-up studies on 181 of the 236 children for periods varying from one to seven years. Only six had abnormalities, as noted in table 4.

In group 4 (controls for group 3) it was possible to follow 196 infants for

TABLE 3

INFANTS WEIGHING 2,500 GM. OR MORE AT BIRTH WITH ASPHYXIA OR DELAYED RESPIRATION

Respiratory delay, minutes	*Neonatal period*				*One to seven years after birth*			
	Normal	*Abnormal*	*Died*	*Total*	*Normal*	*Abnormal*	*Total*	*Not followed*
None	22	5	1	28	23	2	25	3
1 - 5	97	7	0	104	91	3	94	10
6 - 10	20	1	2	23	18	0	18	5
11 - 15	5	4	1	10	7	0	7	3
16 or more	0	0	7	7	0	0	0	7
Not stated	14	2	2	18	15	1	16	2
Total	158	19	13	190	154	6	160	30
Per cent	83.2	10.0	6.8	100	96.3	3.7	100	

TABLE 4

INFANTS HAVING ASPHYXIA OR DELAYED RESPIRATION, WITH CONTROLS: ONE TO SEVEN YEARS AFTER BIRTH

	Asphyxia or delayed respiration			*No asphyxia*		
	No.	*Per cent*	*Follow-up condition*	*No.*	*Per cent*	*Follow-up condition*
Normal infants	175	96.7		190	96.9	
Abnormal infants	6	3.3		6	3.1	
Mongolism	1		Same			
Strabismus	1		Same	2		Same
Questionable "cerebral palsy"	1		Normal at 2½ yr.			
Asymmetry of sterno-cleidomastoid muscles	1		Same			
Mental retardation with strabismus	1		Same			
Convulsion with fever	1			2		Normal at 5 yr.
Congenital heart lesion				1		Same
Convulsive disorder				1		Petit mal, onset at 3 yr.
Total	181			196		

periods varying from one to seven years. As in group 3, there were six abnormal infants (table 4).

Comment on Groups 1 to 4. From follow-up studies of 402 infants born subsequent to prolonged labor and of 236 infants born with asphyxia or delayed respiration, we have found no evidence, in those infants who survived, of any neurologic abnormality due to difficulties encountered during birth. This applies to premature as well as full-term infants.

Of the babies who were born subsequent to prolonged labor or with asphyxia and who were followed, nine (1.7 per cent) suffered from convulsions with fever in early childhood. All nine of these infants appeared normal and well at ages varying from two to five years.

Among the babies who were born after a relatively short uncomplicated labor, 12 had convulsions with fever and three had repeated convulsions without fever. One of the latter died during an attack. One began to have convulsions at five years of age and one had petit mal which started at the age of three years. Thus 2.8 per cent of these children had convulsions. This is in contrast to the former groups (born after prolonged labor or with asphyxia) in which 1.7 per cent had convulsions. In the former groups none had recurring convulsions but these children require further observation, as convulsions may occur in later years. More children with convulsions appeared in the control group than in the group in which labor was prolonged.

EFFECT OF PLACENTAL OR CORD CHANGES

In this group of 4,464 infants born to their 4,411 mothers, there were 104 cases in which the placenta was abnormal and 29 cases in which the cord contained a true knot or was prolapsed. In table 5, the neonatal condition of the babies and the neurologic findings beyond one year on these infants are tabulated for each group.

TABLE 5

INFANTS WHOSE BIRTHS WERE ASSOCIATED WITH PLACENTAL OR CORD CHANGES

	Neonatal condition of infant					*Neurologic findings beyond one year*			
							Children		
	Normal	*Abnormal*	*Still-born*	*Died*	*Total*	*Average years followed*	*Total*	*Normal*	*Ab-normal*
Placental findings									
Abruptio placentae	29	1*	9	3	42	5.5	23	23	0
Placenta previa	20	1†	4	4	29	5.9	19	18	1§
Circumvallate placenta	24	1‡	2	6	33	4.6	21	20	1‡
Total	73	3	15	13	104	5.3	63	61	2
Cord findings									
True knot	14	0	0	0	14	5.1	9	9	0
Prolapsed cord	10	0	3	2	15	4.7	9	9	0
Total	24	0	3	2	29	4.9	18	18	0

*Mongolism.
†Asphyxia pallida; normal at 6 years of age; normal electroencephalogram.
‡Retrolental fibroplasia.
§Strabismus at 6 years of age.

Twenty-eight of the infants born to the 104 mothers with abnormal placentas were stillborn or died. One infant had mongolism, one had asphyxia pallida but was normal at six years of age, and one had retrolental fibroplasia. The remaining 73 were normal. In the follow-up of 63 of these children, one was found to have strabismus, the retrolental fibroplasia in one persisted, of course, while the remaining 61 children were normal.

Among the 29 cases in which the cord was knotted or prolapsed, five infants were stillborn or died. There were no neurologic abnormalities observed in the neonatal period nor among the 18 children that were followed for periods varying from one to seven years. It appears that placental or cord lesions did not cause neurologic lesions in those children who survived.

TOXEMIA OR HYPERTENSION IN THE MOTHER DURING PREGNANCY

One of us (Hunt) reviewed the maternal histories during pregnancy and classified those cases of toxemia or hy-

TABLE 6

INFANTS OF MOTHERS WITH TOXEMIA OR HYPERTENSION OR BOTH DURING PREGNANCY

Maternal diagnoses	*Neonatal findings in infants*					*Neurologic findings beyond one year*			
							Children		
	Normal	*Ab-normal*	*Still-born*	*Died*	*Total*	*Average years followed*	*Total*	*Normal*	*Ab-normal*
Mild toxemia	111	0	6	3	120	5.0	99	98	1*
Severe toxemia	16	0	7	1	24	5.0	15	14	1†
Eclampsia	1	0	2	0	3	0	0	0	0
Chronic hypertension with toxemia	18	0	7	1	26	4.9	10	10	0
Hypertension only	24	0	4	0	28	5.4	20	20	0
Total	170	0	26	5	201	5.0	144	142	2
Per cent	84.6		12.9	2.5				98.6	1.4

*Convulsion with fever at 2½ years of age.
†Harelip, retrolental fibroplasia, convulsion with fever. This child died in a convulsion in 1950.

pertension or both as shown in table 6. Two hundred and one infants were born to these mothers. Thirty-one of these were stillborn or died during the neonatal period, which is a much higher incidence than was observed among the infants born to the controls. The remaining infants were all normal. We were able to follow 144 infants for an average period of five years. Only two abnormal infants were found. One had a convulsion with fever and the other had a harelip, retrolental fibroplasia and convulsions. This child died in 1950. His mother had had severe toxemia. It is unlikely that either of these were abnormal as the result of injury during birth. It would appear that in this group of children toxemia or hypertension or both in the mother did not cause neurologic lesions in children who survived.

SUMMARY AND CONCLUSIONS

1. Among 4,464 infants born in the years 1944 through 1947, 57 (1.3 per cent) had clinical or pathologic lesions which affected the nervous system primarily. Only five of these had difficult births; three of them died and two, while presenting early symptoms, developed normally through the first 12 to 15 months. It is concluded that in this group of 57 infants difficulties during delivery had very little to do with persistent neurologic abnormalities in the infants who survived.

2. In this group of infants we have found no evidence that prolonged labor, asphyxia, or delayed respiration caused any neurologic abnormality in those infants who survived. This applies to premature as well as full-term infants. During the first seven years of life, there were fewer convulsions in the group in which there were prolonged labor and asphyxia than among the controls.

3. Placental or cord changes, as well as toxemia or hypertension, or both, in the mother during pregnancy, did not appear to cause persistent neurologic abnormalities in the children who survived.

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CLINICAL PATHOLOGIC CONFERENCE

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PRESENTATION OF CASE

A 32 year old colored female was admitted to the neurology division of the Philadelphia General Hospital on April 25, 1951, complaining of pains in the legs. The onset of her illness occurred in 1948, nine months after the delivery of a child by cesarean section under spinal anesthesia (the cesarean section having been necessary due to a pelvic deformity). At that time pain between the shoulders was noted and was soon followed by progressive numbness, stiffness and weakness of both legs. The patient entered another hospital in 1948 where myelography demonstrated a sharp abrupt block at T-2, as well as some irregularity of the opaque column at T-4 on the left side. An operation was suggested to the patient at that time but she refused.

After leaving that hospital weakness progressed and flexion contractures of the lower extremities developed, associated with severe pain in the legs. Within one year she became bedridden. Two months prior to admission to the Philadelphia General Hospital she began having involuntary movements of both legs and urinary incontinence, and one month prior to admission the legs became edematous.

Past history revealed that, during the pregnancy noted above, serologic evidence of syphilis was found and the patient was treated with 2,800,000 units of penicillin. There was no other significant history except for the fact that the patient had walked with a slight limp favoring her right leg all her life.

General physical examination showed a young colored woman with pulse rate of 110 per minute, temperature of 99° F., respirations of 20 per minute, and blood pressure of 150/85. The rest of the physical examination was normal except for an aortic systolic murmur.

Neurologic examination showed no cranial nerve abnormality except for nystagmoid movements on lateral deviation of the eyes. The motor functions of the upper extremities were normal but the lower extremities were paralyzed, with the right leg fixed in flexion and the left leg fixed in extension. Both lower extremities were subject to adductor spasm as well as intermittent involuntary movements, apparently withdrawal reflexes. In addition, wasting of the lower extremities was noted. The deep reflexes were normal in the upper extremities but hyperactive in the lower extremities, and the Babinski sign was present bilaterally. Sensory examination revealed a hypalgesia below T-2, with loss of position sense in the feet and legs.

Laboratory examination showed 10.2 gm. of hemoglobin per 100 cc.; the white blood cell count was normal as were the fasting blood sugar, blood urea nitrogen, and the urinalysis. Both blood and cerebrospinal fluid Wassermann tests were negative. On

lumbar puncture the initial pressure was 30 mm. of water, and jugular compression produced a very slow rise to 50 mm., indicating almost complete block. Examination of the cerebrospinal fluid revealed a white blood count of 15 cells per cu. mm., 62 per cent of which were lymphocytes; the cerebrospinal fluid protein was over 200 mg. per 100 cc. X-rays of the spine on April 30, 1951, showed no abnormalities except for residual opaque medium in the cervical and lumbar regions. X-rays of the spine on May 31, 1951, demonstrated the loss of the intervertebral space between T-1 and T-2. X-ray of the chest was normal.

Clinical course: Although an exploratory laminectomy was again recommended to the patient, she refused operation. The patient's condition followed a progressive downhill course, hastened by the appearance of decubitus ulcers, and terminated by bronchopneumonia on December 1, 1951, seven months after admission to the hospital.

DISCUSSION

DR. OLIVERA (neurology resident): We have to think of a spinal cord tumor as well as a herniated intervertebral disc. Another consideration would be a chronic infection, such as tuberculosis or syphilis which might produce a chronic arachnoiditis.

DR. COOPER (medical resident): My first diagnosis would be that of primary involvement of the vertebral column with subsequent cord damage. Herniation of a nucleus pulposus seems to be a likely possibility; however, the complete block, progressive symptomatology and high cerebrospinal fluid protein makes an intraspinal tumor, probably an extramedullary neoplasm, a stronger possibility.

DR. ALDABA (neurology resident): My first consideration in this case would be an intraspinal tumor. As for a herniation of an intervertebral disc, I can't see how this condition could progress for three years and cause the death of the patient. I noticed that serologic evidence of syphilis was found during the patient's pregnancy in 1948. Perhaps an extramedullary granuloma of syphilitic origin should be considered here.

DR. LEVY (intern): The diagnosis of herniated intervertebral disc would be unlikely, due to the fact that normal x-rays of the spine were noted during the first four years of her illness.

DR. SCHUCTER (intern): A herniated intervertebral disc would be an unlikely lesion at that level, and I would think a tuberculous lesion more likely.

DR. PETERMAN (intern): If there had been any infection introduced during the spinal tap at the time of the cesarean section, perhaps a localized infectious arachnoiditis in the upper thoracic area could have been produced. However, one would expect an increased cell count in the cerebrospinal fluid at that time.

DR. SCHLEZINGER (visiting chief of neurology): In approaching the problem of diagnosis it is important to start on an anatomic basis. There is little doubt that this patient has signs and symptoms indicative of an almost complete transverse myelopathy involving the upper thoracic segments of the spinal cord with a sensory level at T-2 dermatome. This localization was verified relatively early in the course of her illness by opaque myelography. The latter showed an almost complete block at the level observed clinically. Therefore, the symptoms and signs are adequately explained on the basis of the anatomic localization just described.

Once one has determined the anatomy he may turn to a consideration of the etiologic factors. I believe that this patient has an intraspinal expanding lesion. The course of her illness is a progressive one, a cardinal feature in an expanding lesion. There is a block shown by the Queckenstedt test and by the myelogram, and the laboratory data suggest an extramedullary tumor. I do not see anything in this clinical picture that is incompatible with that possibility. The x-ray of the spine might perhaps give some cause for hesitation, but it is known that very late in the course of illness a

tumor within the spinal canal may extend to the spinal column and cause destructive changes.

The past presence of syphilis would make it necessary to consider the possibility of adhesive arachnoiditis or an extramedullary granuloma such as an epidural gummatous infiltration. Another type of expanding lesion would be a tuberculous granuloma, but early involvement of the vertebrae would be expected in almost all instances. Occasionally, however, one may find that x-rays of the spine remain negative in the presence of an epidural tuberculous lesion. While it is felt that such tuberculous lesions do originate in the spine, they may originate in parts which are not readily discernible by x-ray, that is, in the laminae and the arches rather than the bodies of the vertebrae. There are many other types of expanding lesions which could be mentioned, and even a herniated disc would have to be considered as a remote possibility. However, it is rather difficult for me to conceive of a primary disc lesion in this case without early x-ray changes. I am not going to mention the various kinds of spinal cord tumors since any textbook of neurology may be consulted for this purpose. I don't think that is the chief problem in approaching a patient clinically; the problem is first to localize the lesion and second to determine whether that lesion is potentially remediable by means of surgery. I believe in this instance the clinical approach was appropriate; the localization of the lesion was established, a provisional diagnosis of an intraspinal expanding lesion was made, and on two occasions the patient was advised to have an operation. In most of such instances an intraspinal tumor will be found.

DR. SOLOMON (chief of the neurology division): In effect the diagnosis boils down to an intraspinal expanding lesion at T-2. The numerous pathologic possibilities of such a lesion would be narrowed down if one could definitely say whether this intraspinal lesion is extramedullary or intramedullary. Dr. Schlezinger feels that it is extramedullary but I am not sure on what basis that differentiation was made. Although the patient did have pain between the shoulders, it was not of the radicular character seen in extramedullary tumors. Such differentiation is always difficult, especially since extramedullary lesions can cause syndromes exactly like those of intramedullary lesions by compressing the vascular supply of the cord. In this case, I would lean as much towards the diagnosis of an intramedullary tumor as an extramedullary tumor. I used the term "tumor" in its widest sense, but if this patient had an intramedullary neoplasm, I believe it would most probably be a glioma.

There were two other points in the previous discussions that I would like to comment on. Someone indicated that the high cerebrospinal fluid protein indicated a tumor rather than any other type of lesion. I believe the high cerebrospinal fluid protein was merely the result of the complete cerebrospinal fluid block. The diagnosis of arachnoiditis was fairly well ruled out on myelography because the configuration of the opaque column in arachnoiditis looks entirely different from that produced by a tumor.

DR. SCHLEZINGER: The possibility of glioma raises a question here. Dr. Solomon has indicated that an intramedullary tumor should be considered. I think these are the important points to remember. Pain is not a reliable distinguishing feature, and one should give that up as a basis for distinguishing intramedullary tumors from extramedullary tumors. Typical root pain may occur in the former and be absent in the latter. I think one is better off relying upon the

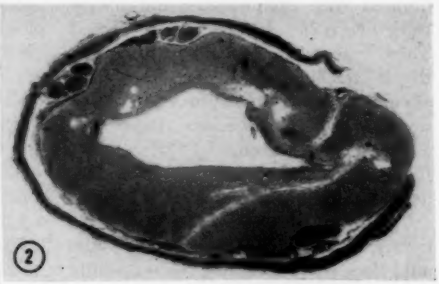

FIG. 1. Dural and Epidural Granuloma. Direct extension into cord substance in right ventral area. Loss of normal cord architecture with focal perivascular collections of lymphocytes and plasma cells.

FIG. 2. Syringomyelic cavity—thoracic cord below level of hypertrophic pacchymeningitis.

whole clinical syndrome. An intrinsic lesion within the cord would be expected to produce dissociated sensory disturbances as in syringomyelia. The tract sensory disturbances here are more consistent with an extramedullary tumor.

Clinical diagnosis: Intraspinal tumor at the second thoracic level.

PATHOLOGIC FINDINGS

DR. RIGGS (chief of neuropathology): The anterior epidural surface of the cord from T-1 to T-3 was fused to the periosteum by a white gristle-like mass of tissue. The anterior half of the dura was thickened for several segments above and below this mass. The entire cord was swollen and fitted tightly within the dural sac. Section at the level of the epidural mass showed obliteration of the subdural and subarachnoid spaces over the anterior half of the cord. The cord substance was soft and necrotic with central cavitation.

In the mid-thoracic region there was a small, irregularly shaped sharply marginated cavity below the gray commissure, extending into the posterior column. This extended through two cord segments. Secondary tract degeneration was present above and below the level of myelomalacia in the upper thoracic cord. Vertebral bone at the level of the lesion showed no gross changes. The general necropsy revealed two chronic peptic ulcers of the duodenum, one of which showed perforation. General peritonitis was present. No evidence of tuberculosis was noted.

Histologic studies demonstrated a localized hypertrophic pachymeningitis in the upper thoracic region (figure 1). This consisted of acellular scar tissue containing focal granulomata and mild diffuse perivascular infiltration with lymphocytes and plasma cells. The granulomata showed a central core of necrotic polynuclear leukocytes surrounded by chronic inflammatory cells and young connective tissue elements. A solitary foreign body giant cell was noted in two of these lesions. The cord at this level contained three discrete granulomata, one of which was continuous with a similar lesion in the dura. The granulomata were surrounded by dense bands of acellular connective tissue. The necrotic cord substance was diffusely in-

filtrated with lymphocytes and plasma cells. Perivascular cuffing was noted. There was no inflammatory exudate in the subarachnoid space elsewhere. The circumscribed cavity in the mid-thoracic region was a typical syrinx ringed with a dense mat of fibrous glia (figure 2). It extended into the anterior horns and deeply into the posterior columns.

The vertebral bone at the level of the hypertrophic pachymeningitis showed mild localized sclerosing osteomyelitis. Examination of the granulomata revealed no fungi or tubercle bacilli.

Pathologic diagnosis: Myelomalacia due to hypertrophic pachymeningitis secondary to epidural abscess. Intramedullary abscess. Syringomyelia.

GENERAL DISCUSSION

DR. SCHLEZINGER: If one has approached the diagnosis in the manner I described there should be no reason to feel dissatisfied. There was evidence of an expanding lesion within the spinal canal. The changes within the spinal cord are not unexpected, beyond the finding of syringomyelia, since there usually is extensive damage to the spinal cord with an extramedullary mass lesion on the basis of circulatory inadequacy as well as direct compression of the cord. I would think that in this case it would be more the former than the latter. The lesion has been referred to as a granuloma. These are always the most difficult lesions to diagnose clinically unless a very clear-cut etiologic factor is present. We might think of tuberculosis which commonly produces an epidural granuloma. Although the patient had syphilis the features of this case do not entirely conform with the diagnosis of a gumma. Does Dr. Riggs feel that she can absolutely rule out a tuberculous lesion?

DR. RIGGS: We can rule out the ordinary type of tuberculosis on the basis of lack of bone involvement.

DR. SCHLEZINGER: Non-specific epidural granulomas do occur every once in a while to baffle us clinically. These produce a chronic progressive inflammatory process which upon histologic examination do not represent any specific lesion such as tuberculosis or syphilis and are not suppurative. One also should consider a neoplastic process such as Hodgkin's disease which also may produce an epidural mass. In this case we have an unusual basis for a rather common clinical syndrome. One would question here what surgery could accomplish. In retrospect it is possible that in the early course of her illness surgery might have been of considerable help, especially if we agree that the damage to the cord was primarily circulatory.

DR. COOPER: Do you think that the penicillin therapy given for syphilis may have influenced the nature of the epidural lesion, and if she hadn't received penicillin would this have evolved into a pyogenic abscess?

DR. RIGGS: Pyogenic epidural abscesses are pretty rare; if they are acute they are seen by the neurosurgeon and evacuated. If the patient is not treated surgically and survives, they go on to scar formation of the type seen here.

DR. SOLOMON: Was this extramedullary process limited to the epidural space?

DR. RIGGS: It was both epidural and intradural. At the time of death there had been such a degree of pachymeningitis that it was impossible to say whether it started within or outside the dura. There were abscesses both on the outer edge of the dura and within the dura itself.

DR. SCHLEZINGER: Would you then call this a hypertrophic pachymeningitis?

DR. RIGGS: Yes. Hypertrophic pachymeningitis due to syphilis was first considered because of the extensive connective tissue overgrowth and the location which is more common in syphilis than in epidural abscess. On the other hand,

the centers of these granulomata contained polynuclear leucocytes giving a histologic picture similar to that of chronic abscess. Dr. Schlezinger asked about tuberculosis. Tuberculosis commonly produces an epidural granuloma secondary to Pott's disease of the body of the vertebra. Even though X-ray may not demonstrate it early, extensive necrosis of the body of the vertebra is usually present. Tuberculous pachymeningitis is a relatively fulminating disease clinically and pathologically. The distinctive feature here was a very massive proliferation of scar tissue which is against tuberculosis.

DR. COOPER: Do we usually see a focus in the vertebra for epidural abscesses, or are they more likely embolic lesions?

DR. RIGGS: Epidural abscesses are usually metastatic rather than the result of direct extension.

Convulsions that are limited in extent or commencement constitute a focal symptom, and indicate disease in or near the motor region, especially the motor region of the cortex. In general convulsions the loss of consciousness is sudden and immediate; there is usually no aura. In partial convulsions, consciousness is lost late, and the patient is usually aware of the local onset. This local onset is due to the fact that the discharge begins in the centre irritated—for the face, arm or leg. If very slight, it may not spread to the corresponding part. If more severe, it spreads to all the centres of the hemisphere, and the convulsion affects the whole of one side of the body. If still more severe, the discharge spreads to the other hemisphere, and the limbs of the other side are also involved, usually after the first side, sometimes, in the most severe fits, simultaneously. Consciousness is usually retained throughout when the convulsion is confined to one limb; sometimes when it involves the whole of one side; scarcely ever when both sides are involved. Different discharges vary in intensity, and the patient often has slight attacks that are local, and more severe attacks that begin locally and become general. The attack usually commences by clonic spasm, which often becomes tonic if the convulsion becomes severe. The spasm almost always begins in the extremity of the limb. But it is common for a sensory "aura" in the part to precede the spasm; the sensation may pass up the limb first affected, along the side of the trunk, and down the second limb affected, and only then may spasm be added. It is as if the discharge commenced in the sensory cells of the cortex, passed like a ripple through these sensory centres, and only when it reached their limit was deflected to the motor cells. In the very slightest attacks the sensory aura may be accompanied, not by spasm, but by the opposite condition—sudden powerlessness of the limb.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published 1885.

CASE REPORT

Occlusion of the Basilar Artery

An Unusual Case With Recovery

Irving Freeman, M.D., Wilber R. Ellis, Jr., M.D. and Lawrence J. Knox, M.D.

Occlusion of the basilar artery of the brain is a rare clinical entity. Although the majority of cases result fatally, one must not assume that this is necessarily true. Kubik and Adams[1] in 1946 reported 18 cases with autopsy findings and an additional four cases which recovered. It was pointed out that the recovered cases had symptoms sufficiently resembling those of the autopsied cases to make the diagnosis almost certain. Prominent clinical features of these cases included suddeness of onset with initial symptoms of headache, dizziness, confusion, or coma. Dysarthria and unilateral paresthesias were also frequent. Other common findings included pupillary abnormalities, disorders of ocular movements, facial palsy, hemiplegia, and/or quadriplegia with bilateral extensor plantar reflexes. Cerebrospinal fluid was normal in every instance. Temporary improvement was common but in the majority of cases, death occurred within two days to five weeks after the onset.

Biemond[2] reported four cases of basilar artery occlusion in 1951. The neuropathology in one of these cases was reported in considerable detail with serial sections of the brain. The author pointed out the lack of a clearly delimited complex of symptoms in this disease because of the varying distribution of softening. He stated that "the major syndrome always remains in keeping with the main localization of the softening; namely, tetraplegia with dysarthria and dysphagia." He reported a case in detail wherein clinical findings were exclusively those of the major syndrome.

The case reported here presents most of the clinical features of a basilar artery occlusion with symptoms and signs of a severe nature and a rather marked degree of recovery.

From the department of medicine, Veterans Administration Hospital, Fort Howard, Maryland.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

CASE REPORT

A 40 year old white bartender was admitted to the Fort Howard Veterans Administration Hospital on September 3, 1950, in a semicomatose state. About four days previously he had complained of headache and dizziness lasting an hour. He was apparently well thereafter until five hours before admission when he suddenly became disoriented and dysarthric, and developed generalized tonic and clonic convulsive movements with salivation and urinary and fecal incontinence.

The past history revealed excessive alcohol ingestion for years, the patient drinking from eight to ten bottles of beer daily. There was no history of trauma or of exposure to, or ingestion of, poisons.

On admission, the rectal temperature was 99.4° F.; the pulse, 64; respirations, 20; and blood pressure, 130/90. The patient was a well developed and well nourished man who was able to move only his eyes in response to his name. He was unable to swallow and salivation was profuse. The pupils were pinpoint in size and reacted sluggishly to light. The gag reflex was absent. All of the extremities were flaccid. The deep tendon reflexes were normally active and equal. The plantar responses were of the extensor type bilaterally. Abdominal and cremasteric reflexes were absent. There was questionable slight nuchal rigidity. The teeth were tightly clenched. Five hours later the deep reflexes were hyperactive bilaterally and there was no nuchal rigidity.

A lumbar puncture yielded clear, colorless fluid under 210 mms. of water pressure. The protein content was 30 mg. per 100 ml. No cells were observed microscopically. A complement fixation test and colloidal gold curve were negative. The hemoglobin was 14.2 grams per 100 ml. The white blood cell count was 11,400 per cu.mm. with a normal differential. The urine had a specific gravity of 1.003 and contained a trace of albumin and 20 to 25 red blood cells per high powered field. The Eagle flocculation test was negative. The sedimentation rate (Cutler) was 17 mms. per hour. The blood sugar was 100 mg. per cent and the NPN, 55 mg. per cent. An x-ray of the skull revealed no abnormalities. An electrocardiogram and chest roentgenogram were normal.

During the first 48 hours of hospitalization the patient had a series of generalized convulsions. On September 4 he responded to questions by moving his eyes in the direction of the speaker. He was able to wrinkle his forehead slightly. His temperature rose to 102° F, rectally, and remained at this level for seven days. Profuse diaphoresis was evident for a period of two weeks. The patient was maintained on a 3,000 calorie liquid diet administered via a Levin tube. Aureomycin, 0.5 Gm. every six hours, was administered through the tube. An indwelling catheter was inserted. Nasal suction was applied at four hour intervals for removal of accumulated oropharyngeal secretions.

On September 13, physiotherapy, in the form of passive motion of all extremities, was instituted. By October 15 sufficient return of the swallowing function was evident to permit the patient's taking liquid without the aid of a stomach tube. Minimal spontaneous movements of the left upper extremity and extension of both knees were noted. The patient was able to make groaning sounds but could not articulate. By November 1, he was supported in a wheelchair. More spontaneous motion was evident in the entire right arm. By the middle of December some motion was apparent in all four extremities. The indwelling catheter was removed with permanent return of voluntary bladder control. On January 2, 1951, he was able to utter a few words. Intensive physiotherapy consisting of infrared light application, electrical muscle stimulation, speech training, and ambulation with the use of crutches was instituted. By March 27 he was able to walk around his room with the aid of crutches and could eat and dress himself without assistance. He was discharged from the hospital on this date.

He was readmitted on June 28, 1951, because of pneumonia, presumably due to aspiration. A chest x-ray revealed bilateral basilar infiltration. The infection promptly responded to penicillin. His general condition had not changed from that of the time of his discharge other than a complaint of slight difficulty in swallowing. Neurologic examination revealed a slight sagging of the right side of the mouth, diminished motor power in the right hand and right side of the mouth, and diminished motor power in the right hand and right leg with spasticity in both of the limbs. There was slight flattening of the thenar and hypothenar eminences of the right hand. The deep reflexes were more active on the right. The Hoffmann sign was positive bilaterally. There

were faint superficial abdominal responses but the cremasterics were absent. The plantar responses were of the extensor type. To this date, there has been no appreciable change in this individual's condition.

DISCUSSION

This patient presented the premonitory symptoms of dizziness and headache several days prior to the major episode. The latter consisted of an acute onset of tetraplegia with aphagia and anarthria, following generalized convulsions. Trismus, facial diplegia, pinpoint pupils, hyperactive deep reflexes, and extensor plantar responses were likewise part of the clinical picture. Extraocular muscle palsy was conspicuously absent.

This case presented more evidence of extensive involvement than previously reported cases with recovery. Prevention of secondary infection by appropriate antibiotic treatment, and intensive physical therapy were largely responsible for the survival of the patient with maximum return of function.

SUMMARY

A clinical case of basilar artery occlusion with complete tetraplegia, facial diplegia, and "pseudobulbar palsy" with a marked degree of recovery is presented. The literature is reviewed briefly. The favorable outcome of this case makes it mandatory to expend every effort to rehabilitate such cases.

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The characteristic, then, of the convulsions of organic brain-disease is their local commencement. Whether the fit remains limited to the part in which it commences, or spreads to other parts, even the whole body, is a question of degree. Moreover, a local aura, without convulsion, has the same significance as local spasm. It indicates that the discharge commences at one part of the brain, that there is at that part a morbid state, and it is thus a focal symptom. Convulsions that are general from the first are often due to, and symptoms of, organic brain-disease; but they derive their significance from associated symptoms, idiopathic epilepsy, not the organic brain-disease that local commencement suggests. I say *suggests*, because there is sometimes a local commencement in idiopathic epilepsy in such a case unless you had ascertained that other symptoms of organic brain-disease were absent, and you could not feel confident, unless the convulsions had existed alone for a considerable time, or there was a strong family tendency to the idiopathic disease.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published 1885.

CASE REPORT

Congenital Toxoplasmosis

John Moossy, M.D. and H. W. Gillen, M.D.

THIS report deals with a case of serologically-confirmed congenital toxoplasmosis in an adolescent boy. There are some unique features that might profitably be brought to the attention of neurologists.

The ubiquity of the disease, the nature of the protozoan parasite, Toxoplasma, the wide range of animal hosts and the numerous unsuccessful attempts at therapy have received increasing attention in the literature. Although pathogenetic concepts are not yet adequate it is felt that the disease manifests itself in one of three forms in man. It may be acquired by children or adults, or it may be an *in utero* infection, i.e., the congenital type. A distinct clinical picture is presented by each type with some modifications depending upon the acuteness, chronicity or latency of the infectious process. The predilection of Toxoplasma for the fetal neuro-ectoderm produces rather obvious signs of neural and ocular dysfunction.

CASE REPORT

A 13 year old white boy was first seen in the neurologic clinic on July 16, 1951 because of convulsions.

Present illness: The first convulsion occurred during sleep on June 16, 1951. His mother noted that he was "stiff, had his teeth clenched, was green about the mouth, and his eyes were staring ahead." He did not respond to stimuli for about ten minutes. On waking he had amnesia, both recent and remote, lasting about one hour. He was taken to a hospital where it was observed that he seemed very excited. He was given an injection intramuscularly, and was sent home.

On July 11, 1951 he had a short period of numbness and stiffness of his right hand. Three days later the patient, while standing, suddenly stopped talking, did not fall, was out of contact, was "green around his mouth," and then returned to consciousness, again having amnesia for the episode and for the preceding few hours. He was brought to the neurologic clinic for evaluation. During the first examination in the clinic the patient had a short episode not unlike petit mal epilepsy.

Past history: There were no previous or subsequent pregnancies according to the mother. She could recall no illnesses during pregnancy and she had had no animal contacts at any time.

The patient's birth was normal and without complications, after an uneventful gestation of nine months. The child developed normally until the age of six months when his mother noted that he did not see things well, and his eyes "jumped all the time." He talked at 14 months, and used complete sentences at 24 months. He continued to present the problem of decreased visual

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Read at the fourth annual meeting of the American Academy of Neurology, Louisville, Kentucky, April 24, 1952.

FIG. 1. Lateral of the pneumoencephalogram showing the ventricular outlines and multiple intracranial calcifications.

acuity, and has been educated as a blind child, attending a special school for the blind. He is in the seventh grade. He reads Braille, including music, and plays the piano and harmonica. During early childhood his only known illness was chicken pox at the age of six years, and the only operation was an uncomplicated tonsillectomy at the age of three.

Family history: The patient is an only child of separated parents, and has been brought up exclusively by his mother. A maternal uncle had occasional grand mal epileptic seizures, always while asleep, from the ages of 13 to 21, and three members of his mother's family had diabetes mellitus.

Physical examination: The patient was a white adolescent youth who appeared older than the stated 13 years. He had a small head, 50 cm. in circumference. He was left handed and occasionally flexed the left arm at the elbow and extended the wrist while walking on his toes. Otherwise the gait was normal. The right arm and wrist were slightly weaker than the left. Movements of the right hand and arm showed slight dyssynergia. The reflexes and the peripheral sensory status were normal. Testing of cortical sensory function revealed excellent perception of the weight, shape and texture of objects. The patient was barely able to count fingers at one meter in both eyes. The right pupil was 5 mm. in diameter, and the left was 7 mm. He had a right convergent strabismus, and a coarse searching nystagmus in all directions. Ophthalmoscopic examination showed bilateral optic atrophy, areas of healed chorioretinitis bilaterally, coloboma of the choroid on the right, and normal blood vessels. He also had microcornea. Laboratory studies were normal.

Stereoscopic x-rays of the skull showed multiple calcifications varying from 1 to 5 mm. in diameter distributed throughout the brain. A pneumoencephalogram demonstrated an essentially normal ventricular pattern (figure 1).

The electroencephalogram showed a bioccipital random spike focus, and bursts of 14 per second positive spikes symmetrically in the temporal, parietal and occipital leads.

Serological studies for toxoplasma were positive with a titre of 1:1024, while those for the patient's mother were positive with a titre of 1:128.

Psychological testing utilizing the verbal scale of the Wechsler-Bellevue Intelligence Scale for Children showed an I.Q. of 80 but with a high score on "similarities."

COMMENT

Since the case presented is believed to be of the congenital type of toxo-

plasmosis this discussion will be limited to the features peculiar to that form.

The organism Toxoplasma is a protozoon found in many wild and domestic mammals, birds and reptiles.[2] Microscopically, the organisms are oval, elliptical or elongated, 2 to 4 microns in width and 4 to 7 microns in length. Nuclei are central or polar in location. The parasite can be located intra- or extracellularly, can be free or in pseudocysts and can invade any tissue in the body. Congenital forms of the disease are characterized by the widespread destructive granulomatous reaction produced by the parasite in the nervous system and eye. Clinical features of the disease, therefore, are chiefly neurologic and ocular. Callahan, Russell and Smith,[2] in a discussion of 18 cases of congenital toxoplasmosis, tabulated neurologic signs and symptoms in order of frequency as internal hydrocephalus, muscular twitchings, convulsions, spasticity, opisthotonus, head retraction, stiff neck and paralyses. Focal chorioretinitis and cerebral calcifications usually detectable by x-ray are constant findings in congenital toxoplasmosis.[2,3,4,5]

Signs other than those of the nervous system include hepatomegaly, splenomegaly, fever, subnormal temperature, pulmonary signs, jaundice, purpuric spots, vomiting, diarrhea and feeding difficulties.[2]

If infants survive, the clinical picture settles down to a more chronic or inactive phase in which residual damage becomes evident. Ocular findings are those of decreased vision, nystagmus, microphthalmus, strabismus and healed or inactive chorioretinitis.[3] Neurologic findings include convulsions, either generalized or of a petit mal type, chronic hydrocephalus, mental retardation and cerebral calcifications by x-ray. Cowen, Wolf and Paige[6] felt that though these patients might live to adult life, mental deficiency was the general expectation. Wyllie, Fisher and Cathie[4] in 1950 reported a case of a five year old girl with serologically confirmed toxoplasmosis who was felt, "to be above average intelligence for her age," despite marked hydrocephalus. They stated that hydrocephalus was one of the four cardinal signs of the disease. They felt that regardless of head size, "all show degrees, often extreme, of ventricular enlargement." While the patient reported here had a small head (50 cm. in circumference), three petit mal-like episodes, searching nystagmus, microcornea, healed chorioretinitis and numerous cerebral calcifications, he had no hydrocephalus as determined by pneumoencephalography. Intelligence was apparently normal, as determined by psychological testing and social and scholastic achievements. The boy has been followed for seven months and no additional seizures have occurred even though the patient has been given no anticonvulsant drugs. His performance in school has been satisfactory. Growth and pubertal development have proceeded normally.

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Neurology BOOK REVIEWS

The Treatment of Injuries to the Nervous System

Donald Monroe, M.D. 1952. Philadelphia & London: W. B. Saunders Co., 284 pages, 47 illustrations, $7.50.

Without a lengthy discussion of theoretical aspects, this book gives a practical and concise account of the treatment of injuries of the nervous system, based upon extensive personal experience. The care of injuries of the head, spine, spinal roots and peripheral nerves is presented in separate sections. A valuable discussion on birth injuries is included. In conclusion Dr. Munro discusses the necessity of cooperation between hospital and medical staff to assure good treatment and rehabilitation of head and spine injuries. A chapter on the cost of medical care for injuries of the nervous system, indicating how it may be modified by a good rehabilitation program, is written by Stanwood L. Hanson. A brief list of references to pertinent papers is given and an adequate index appended.

This is a valuable practical book which should be on the bookshelf of all physicians treating head injuries, for in it may be found the straightforward answers to many problems encountered in such cases. The discussion on the methods of rehabilitation is especially well written and should find a welcome audience.

A. E. W.

Headache

Louis G. Moench, M.D. Second edition. 1951. Chicago: The Year Book Publishers, Inc., 217 pages, $4.50.

This small book, written by an internist and designed chiefly for the medical practitioner, deals with anatomical and physiological mechanisms of head pain as well as diagnosis and treatment. Much important and useful information is compressed within it. The author bases most of the discussion on experimental studies of referred pain published by others and the medical literature is frequently quoted. The many charts and diagrams add greatly to the value of the book, but at the same time they represent its weakest quality. Continuity and clarity are frequently sacrificed because of the many inclusions and references to the experience of others. The chapter on "Migraine," which reflects principally the author's experience is very well done.

This, the second edition, has a number of appropriate additions over the first edition. More space is given to posttraumatic headache, and the psychological aspects of head pain are more frequently mentioned. The final chapter on "Headache of Emotional Origin" is well written and convincing, but it needs to be better correlated with the other chapters. In view of the importance given to psychological factors in this chapter, it is surprising that the treatment sections of other chapters included little or nothing concerning this approach.

A. S. R.

Intracranial Aneurysms

Wallace B. Hamby, M.D. 1952. Springfield, Illinois: Charles C Thomas, Publisher. 524 pages, 193 illustrations, $13.75.

This work represents a painstakingly detailed sifting and analysis of the world literature on the subject as well as the author's own experience represented by 48 cases discussed in detail. It is a handsome volume, done in a brilliant publishing tradition, consisting of seven chapters dealing with cerebral vascular anatomy and physiology, etiology of aneurysms, general and specific methods of diagnosis and treatment of aneurysms, and some general considerations for pre- and postoperative management of these lesions.

The minutae of methods of diagnosis and specific treatment presented holds the key for those who must deal with these dread lesions more or less without assistance.

The author has skillfully rendered a coordinate coalescence of widely varying opinion in condensed form for "pick, weigh, and choose" on the part of the reader—free of dogmatism on his part.

The subject today is indeed embraced by a potpourri of strong-willed individual opinion. For this reason alone the author is to be congratulated for his compilation and coordination of this material, tempered by his meaty but modest cognate asides of real practical worth from his own experience.

The bibliography of 700 references is outstanding. Its accumulation alone represents a scholarly achievement. This volume should be on the "used book" shelf of all neurosurgeons and neurologists. R.C.B.

The Principal Nervous Pathways

Andrew Theodore Rasmussen, Ph.D. Fourth edition. 1952. New York: The Macmillan Company, 73 pages, $4.50.

The first edition of this work appeared in 1932. In this, the fourth edition, the basic pattern remains the same. The extensive experience in teaching graduate and undergraduate students which led to the original plan has proven to be a sound guide. This is preeminently a *precis* for the beginner and advanced student in neuroanatomy. The beginner finds in the grouping of structures of the nervous system into fundamental sensory and motor mechanisms a mode of synthesizing the data acquired in reading and laboratory observation. To the initiated, there is the exciting hunt through the carefully drawn diagrams for the answer to such questions as "What view does Rasmussen take of the proprioceptive components of the eye-muscle nerves?", "How does he handle the vexing problem of special visceral efferent fibers?"

Since its appearance this book has been recommended by the reviewer for supplementary reading in the undergraduate course in neuroanatomy. It is ideal for a review and integration of material for the board examinations in neurology, psychiatry and neurosurgery. Graduate students in all related fields will want it close at hand. The clinician accustomed to its use can quickly find from the diagrams the answer to many a simple or complicated neural connection.

The typography and reproduction of the illustrations is clear and distinct. In addition, the drawings are so carefully made that a hand lens may always be used. A.R.V.

REVIEW COURSES IN
BASIC and CLINICAL NEUROLOGY

APRIL 6, 7, 8, 1953

Preceding the

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Neurology

Studies of the Spinal Cord

Part 3. Pathways for Deep Pain Within the Spinal Cord and Brain

Robert E. Yoss, Ph.D., M.D.

THIS study was undertaken in order to determine more accurately the pathways within the central nervous system which mediate impulses set up by painful stimuli in tendons. The clinician frequently tests for Achilles tendon (and other tendon) insensibility (Abadie's sign). A more profound understanding of the significance and of the neuroanatomic background of deep pain in the interpretation of such clinical signs would be of obvious value.

Furthermore, because of the recent localization studies of the lateral spinothalamic tract for superficial pain,[1–4] it would be worth while to know whether there is likewise such localization in the tract mediating impulses set up by deep pain stimuli.[5] Since deep pain is clinically well localized, there should be a well organized localization pattern in all pathways carrying impulses aroused by such painful stimuli to conscious levels. It would appear that peripheral specificity will be accompanied by a specific pattern of localization in secondary tracts and nuclei within the central nervous system.

PROCEDURE

Three monkeys (Macaca mulatta) were used for these experiments. The most important hurdle in a study of this type is an accurate test to determine

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Part 3 of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

whether or not pain from tendons is recognized under the experimental conditions. This is not easy to determine in experimental animals, such as the monkey, when sometimes even the evaluation of superficial pain is difficult. Pressure over the Achilles tendon, as tested by the clinician, would be invalid in the monkey since any response could have been aroused from the stimulation of the overlying skin as well as from the deeper lying tendon. The tendon, and only the tendon, must be stimulated.

The Achilles tendon was exposed under ether anesthesia in the first animal (monkey No. 31). After a sufficient time had elapsed for the monkey to regain consciousness, and while the animal was still restrained on the operating table, the isolated Achilles tendon was stimulated by pressure caused by clamping a rubber-tube-covered hemostat on the tendon. No response that could be interpreted as pain was obtained when the animal was tested immediately on recovery from the anesthesia. If, however, the wound was closed and the animal allowed 24 hours to recover from the anesthesia and then retested without anesthesia, a very typical and conclusive response to pain was obtained. Testing was done in this manner: The tendon was exposed on the day preceding testing and the wound sutured and dressed using sterile technique. The following day the sutures were removed and the tendon re-exposed without any anesthesia, a procedure that was not particularly disagreeable to the animal. This exposed tendon was then stimulated by the rubber-tube-covered hemostat and the response of the fully-awake animal recorded. (Immediate testing following ether anesthesia was carried out on two occasions in monkeys No. 32 and No. 33, with satisfactory results.)

Lesions in selected portions of the spinal cord (dorsal column; anterolateral column) and in the cerebral cortex (in one case) were produced experimentally and each of the three animals was then retested for deep pain in the above described manner. The extent of the spinal cord lesions was confirmed in Marchi preparations.

CASE REPORTS

Monkey No. 31.—On January 29, 1951, under light ether anesthesia, the Achilles tendon on the right was exposed. When the animal was apparently wide-awake, this tendon was stimulated by extreme pressure applied with a rubber-tube-covered hemostat. No response was obtained from the tendon stimulation after many attempts. The response to painful stimulation of the skin at this time was not marked. The examiners believed that the effect of the ether anesthesia was still present in spite of the apparent normal consciousness.

The animal was again anesthetized, and the left Achilles tendon exposed. Without testing, the wound was closed with close interrupted sutures and properly dressed.

On January 30, 1951, without anesthesia of any kind, the monkey was restrained on the operating table, and, using sterile precautions, the left Achilles tendon was exposed. The sutures from the preceding day were removed without any objection from the animal. However, on painful stimulation of the skin of either upper or lower extremities by pricking with a sharp needle, the monkey gave a clear-cut response which indicated that the stimulus was obviously disagreeable to him. Using a rubber-tube-covered hemostat, the left Achilles tendon was compressed sufficiently hard to have caused pain in man. Each time the monkey gave the type of response seen earlier when the skin had been painfully

stimulated. This was interpreted as a normal response to a painful stimulation of the Achilles tendon.

On February 5, 1951, using intravenous thiopental sodium anesthesia, the cervical region of the spinal cord was exposed. The cord was rotated slightly to the left and a cordotomy performed at approximately C4 on the right side. The section was intended to include all of the dorsal spinocerebellar fibers on the right (for use in another study[6]) and the most dorsolateral portion of the lateral spinothalamic tract on the right. Some pyramidal tract fibers on the right were also involved. It was hoped that all, or at least most, of the dorsal white columns were spared.

On February 6, 1951, the animal showed a right-sided ataxia and had a moderate amount of difficulty getting about in his cage. There was no apparent weakness in any of the extremities.

The unanesthetized animal was secured to the operating frame and the sutures were cut and the left tendon exposed and stimulated with the rubber-tube-covered hemostat; no response was obtained. On stimulation of the right Achilles tendon, and also of the overlying skin, there was a marked, typical response to painful stimuli such as had been obtained in the monkey before the cordotomy had been performed. There was a level of analgesia of the skin on the left to approximately the midthoracic segment.

On February 19, 1951, the wrist tendons were exposed bilaterally under ether anesthesia. The wounds were closed with interrupted sutures.

On February 20, 1951, the wrist tendons were stimulated with the rubber-tube-covered hemostat without using any anesthesia. The animal responded in a way which suggested that the stimulation was disagreeable to him. Then the animal was anesthetized with thiopental sodium and the left frontoparietal cortex was exposed. The motor "arm" area was located accurately by electrical stimulation and a large cortical lesion, which involved not only the sensory "arm" area but a considerable amount of adjacent cortex including that in the depths of the central fissure and part of the "arm" motor area, was produced by electrocauterization.

On February 21, 1951, without any anesthesia, the wrist tendons were re-exposed and stimulated. A typical response was obtained bilaterally, comparable to that elicited before the cortical lesion was made. The animal was then perfused, while under anesthesia, with 10 per cent formalin and the brain and the spinal cord removed.

Postmortem examination disclosed that the cordotomy was at C4. The brain and the spinal cord segments were prepared by the chlorate-osmic-formalin stain.

Resumé of microscopic findings: There was Marchi degeneration of only the dorsolateral portion of the right ventrolateral ascending bundles. In the right dorsal column the degeneration involved the lower lateral part of the field, secondary to section of the right dorsal fourth cervical root. In addition, there was finely scattered degeneration throughout the left ventral and the left lateral white columns and the dorsal half of the right lateral white column of the cord (figure 1a).

Monkey No. 32.—On December 3, 1951, under thiopental sodium anesthesia, the lower cervical cord was exposed in the usual manner. The dura was opened in the midline and the spinal cord was rotated to the right. In order to rotate the cord, a dorsal root on the left was sectioned and the dentate ligament grasped and used in retracting and rotating the cord. A cut was made in the left lateral column immediately ventral to the left dentate ligament; this section was carried ventromedialward to the midline. It was thought to include all of the left ventral column and the ventral half of the left lateral white column; also, the most ventromedial portion of the right ventral white column was involved. When the animal was examined a few hours after the operation, he showed a slight motor deficit in the left lower extremity.

On December 27, 1951, under ether anesthesia, both Achilles tendons were exposed and the wounds sutured and dressed immediately.

On December 28, 1951, the unanesthetized animal was restrained on the operating table and the Achilles tendon re-exposed bilaterally. It was noted that all of the sutures on the right side had been removed by the monkey but the left wound was intact. There was a loss of both superficial and deep pain in the right lower extremity but the response to these modalities was normal when the left lower extremity was tested. Although the animal did not react when tested on the right side, the observers felt that he was aware that the tests were being made, even though such tests did not appear to be painful to him.

The animal was then anesthetized and perfused. Postmortem examination disclosed a gross lesion at the level of T1 involving the ventral portion of the lateral white column and the ventral white column on the left up to the midline. The left first thoracic dorsal root had been sectioned.

Resumé of microscopic findings: The spinal cord lesion was located at the first thoracic level, interrupting all fibers between the left dentate ligament and the ventral median fissure and extending medialward into the left ventral gray horn. The dorsal portion of the left lateral white column, as well as the more dorsomedial part of the left ventral white column, were spared. There was some degeneration of the dorsal white column on the left, secondary to the section of the left dorsal first thoracic root (figure 1b). The degenerated dorsal and ventral spinocerebellar fibers were distributed fairly evenly throughout the vermis portion of the anterior lobe of the cerebellum. In addition, there were many degenerated fibers passing to the uvula, the pyramid and the declive.

Monkey No. 33.—On January 9, 1952, under ether anesthesia, the lower cervical cord was exposed. A lesion was made in the most dorsomedial portion of the right dorsal white column to include all the fibers arising from lower extremity levels on the right.

On January 19, 1952, the Achilles tendon was exposed bilaterally while the animal was under light ether anesthesia. The monkey was permitted to regain consciousness. After a short waiting period, each Achilles tendon was stimulated by extreme pressure applied by the rubber-tube-covered hemostat and the skin in the area was tested for superficial pain by pricking with a sharp needle. There were equal and like responses bilaterally to the tests for both superficial and deep pain. The wounds were closed and dressed. Because of the positive bilateral responses there was no need to retest the next day when the effects of the anesthesia had completely disappeared.

On January 30, 1952, the cervical cord was re-exposed while the animal was under light ether anesthesia. A dorsal and a ventral root were sectioned on the right and a section of the cord was made (on the right) which extended from about 2 mm. dorsal to the dentate ligament ventralward to the emergence of the ventral root.

On February 12, 1952, the earlier Achilles tendon exposures had completely healed, so re-exposure was done under light ether anesthesia. After recovery from the ether, the skin and the Achilles tendons were stimulated. No response to this stimulation was obtained on the left side but normal responses were elicited on the right. The responses were not so satisfactory as those exhibited by animals completely unanesthetized but they were nevertheless definite and unequivocal.

Under thiopental sodium anesthesia, the animal was perfused with 10 per cent formalin and the brain and the spinal cord removed. Postmortem examination revealed a small lesion of the right lateral white column of the cord, most marked at the eighth cervical but extending into the seventh cervical level.

Resumé of microscopic findings: The lesion at the seventh cervical segment interrupted all the ascending fibers in the right ventral and the right lateral white columns. There was some degeneration in the left ventral and the left lateral white columns but much of this degeneration was adjacent to the left ventral gray horn and consisted not of long ascending fibers but rather of short intersegmental bundles (figure 1c). The dorsal and the ventral spinocerebellar fibers were distributed predominantly to the anterior lobe of the cerebellum (vermis and medial part of the hemisphere) with perhaps a heavier concentration in the

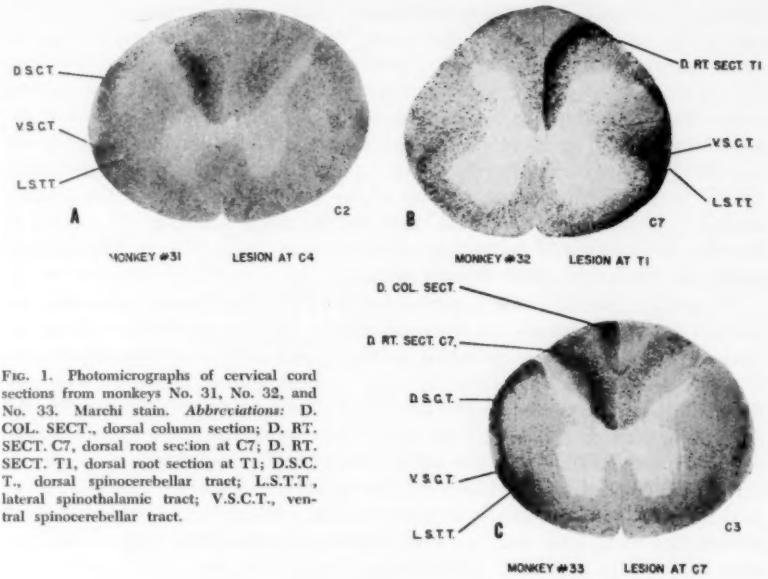

FIG. 1. Photomicrographs of cervical cord sections from monkeys No. 31, No. 32, and No. 33. Marchi stain. *Abbreviations:* D. COL. SECT., dorsal column section; D. RT. SECT. C7, dorsal root section at C7; D. RT. SECT. T1, dorsal root section at T1; D.S.C.T., dorsal spinocerebellar tract; L.S.T.T., lateral spinothalamic tract; V.S.C.T., ventral spinocerebellar tract.

central lobule and lingula than in the culmen. There were also degenerated fibers to the pyramid, the uvula and the declive.

RESULTS

There are indications that impulses set up by painful stimuli in tendons are carried in the lateral spinothalamic tract of the side opposite to the stimulation. In monkeys No. 31, No. 32 and No. 33, there was a complete loss of deep pain when the Achilles tendon was stimulated on the side opposite the unilateral ventrolateral cordotomy that interrupted all, or part, of the constituent lateral spinothalamic tract (figure 1). In addition to the loss of deep pain, tests indicated that superficial pain was not appreciated on the opposite side of the body, beginning below the level of the lesion. The areal extent of analgesia was dependent upon whether the section of the lateral spinothalamic tract was complete. Impulses set up by deep or superficial pain on the side of the lesion reached conscious levels.

In monkey No. 31 section of the lateral spinothalamic tract was incomplete. Approximately the dorsolateral half of the ventrolateral ascending fiber systems on the right was involved at the fourth cervical segment (figure 1a). Deep pain sensibility was absent from the left Achilles tendon but present in the right Achilles tendon and in the wrist tendons of the upper extremities. This indicates that impulses set up by painful stimuli of the tendons of the lower extremity (at least of the Achilles tendon) are carried in the more dorso-

lateral portion of the lateral spinothalamic tract and that probably impulses set up by comparable stimulations in the upper extremity are carried in the more ventromedial (uninterrupted) portion of the tract. Therefore, the findings in monkey No. 31 are highly suggestive of the existence of a like pattern of localization within the lateral spinothalamic tract for deep pain and for superficial pain. The fibers mediating impulses from the tendons of the lower extremity are situated in the dorsolateral portion of the tract, fibers mediating similar impulses from upper regions of the body are located in the ventromedial portion of the tract, and, presumably, fibers functionally related to impulses from intermediate regions of the body are located in an intermediate portion of the lateral spinothalamic system.

In monkey No. 31 (with a partial lesion of the right lateral spinothalamic tract at C4) the possible retention of deep pain was checked in the upper extremities following the operation on the spinal cord; such sensations were found to be present bilaterally. A large cortical lesion (figure 2) was produced in the sensory area on the left side including that portion usually allocated to sensations from the right upper extremity. Following such a lesion, deep pain was still intact in the upper extremities and of the same quality as before the cortical lesion. However, the quality of response was difficult to evaluate, and any evaluation, at best, is crude. In any case, it may be concluded that deep pain reaches consciousness at a site other than in the primary sensory (postcentral) cortical area.

Up to 25 days following complete unilateral ventrolateral cordotomy (monkey No. 32) there is still complete loss of deep pain on the side opposite the lesion and beginning slightly below its level. It is not known whether, after a longer time had elapsed, there would be a partial return of deep pain sensibility by way of ipsilateral pathways of the spinal cord.

Because of the large number of neuromuscular and neurotendinous nerve endings in muscles and tendons, and the possibility that deep pain results from "overstimulation" of such nerve endings, it was felt that the possibility of dorsal column conduction of impulses set up by painful stimulation of tendons should be considered. In monkey No. 33 the dorsomedial portion of the right dorsal column was sectioned in the cervical region (figure 1c). Following this spinal cord procedure and bilateral exposure of the Achilles tendons, both tendons were stimulated by painful stimuli and normal responses to such stimuli were obtained from both of the lower extremities and were of like quality. The dorsal column section was sufficiently complete and at the proper level to interrupt all the fibers of this column that carried impulses arising from the right lower extremity.

The surgical exposure of the Achilles tendons was done prior to central nervous system surgery in monkeys No. 31 and No. 33. However, in monkey No. 32 the cervical ventrolateral cordotomy was carried out first and then followed by tendon exposure. The day after such tendon exposure, when the animal was to be tested for deep pain, it was noted that he had removed all

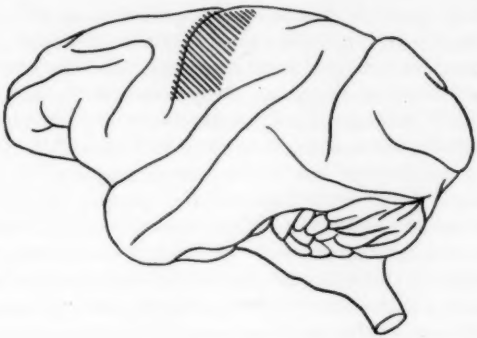

FIG. 2. A diagram showing the extent of the cortical lesion in the left hemisphere of monkey No. 31.

the interrupted sutures from the analgesic side, although the wound on the other leg was intact. This never occurred in the other two animals used in this study in which the wounds were made in skin sensitive to painful stimuli at the time of tendon exposure, even when the wound area subsequently became analgesic as a result of cordotomy.

The observers of the animals during the testing for deep pain thought that the monkey thus tested was aware that something was being done to the analgesic tendon and adjacent tissues but that such stimulation was not disagreeable. This awareness was difficult to evaluate but probably was nothing more than a normal response to tactile stimuli.

DISCUSSION

As was pointed out long ago in the monumental work of Henry Head and his associates,[7–10] there are two mechanisms for the production of pain from somatic structures, one of which is situated in the skin and the other in the deeper structures. It is the latter system which is concerned in this study, but it should be emphasized that any investigation must be cognizant of these two pathways or else the interpretations may be justly subjected to criticism.

This inquiry was undertaken, not because the observations of Head and his associates were inadequate – since, indeed they were not – but because new aspects to the problem of deep pain have arisen as its clinical importance has received wider attention. As the knowledge of the localization pattern for superficial pain in the lateral spinothalamic tract has increased, the question has arisen whether a similar arrangement holds for fibers mediating deep pain. Obviously experimental work affords a useful approach to this problem.

The deep sensibilities are those modalities carried not in cutaneous peripheral nerves but in the sensory components of muscular nerves. Head and Sherren,[8] Trotter and Davies[11] and others have demonstrated that, following section of all cutaneous nerves to a given area, there are still several sensory modalities present in the underlying tissues, such as deep pain (deep pressure

pain), pressure, tactile sense, position sense and vibratory sense, which are carried in the muscular nerves. The term, deep pain, is used here for pain arising from deep somatic structures rather than for pain from viscera as Harman[12] applied the term. Deep sensibility is lost by peripheral lesions only when a muscular nerve, or the dorsal root giving rise to the sensory components of such a nerve, is sectioned. Then, all the modalities of the deep sensory system are lost in the tissues supplied by the sectioned nerve. Lehmann[13,14] and Shaw[15] were of the opinion that all deep pain is conducted to the spinal cord by way of the ventral roots and Shaw even demonstrated, to his own satisfaction, such ventral root conduction in an experimental animal (rabbit). However, the studies of these latter observers are largely discounted because of the overwhelming evidence that impulses set up by both superficial and deep painful stimuli are carried from the area innervated over fibers which enter the dorsal roots.[10,16–19]

It should be emphasized that cutaneous and deep pain arising in a given area of skin and the immediately underlying deep tissues may or may not be innervated by the same dorsal nerve root. It has been pointed out by Head,[10] Lewis,[19] Sinclair, Weddell and Feindel[20] and others that there may be a considerable discrepancy, especially from extremity regions, between the levels of innervation of a cutaneous area and that of the adjacent deeper lying somatic tissues.

The characteristic pain arising from tendons is usually considered to be sharp and well localized (Waterston;[21] Kellgren,[22] and Weddell and Harpman[23]), although Lewis[19,24] and Smith[25] have described it as of a diffuse and dull aching type but fairly well localized to a given tendon. However, the work of Weddell and Harpman[23] has been criticized by Feindell, Weddell and Sinclair[26] because of the possibility that the cutaneous nerve endings overlying the stimulated tendon may not have been completely anesthetized. This objection has been eliminated in the present study by direct stimulation of the tendon. According to Weddell and Harpman,[23] deep pain can be best aroused from tendons near their musculotendinous junction. It should be emphasized that all pain arising in somatic structures is not necessarily somatic pain (superficial or deep) because it may be visceral pain from the region about blood vessels and, therefore, subject to different conditions.

In tendons, there are free nerve endings which apparently are aroused by deep painful stimuli.[23,26]. These endings are associated with the Golgi tendon endings and may be collaterals of the sensory fibers to the organ of Golgi. The function of such an "accessary" innervation has been suggested by Woollard[27] to be that of protection of the "principal" receptor (Golgi organ for position sense stimuli) from damage. Weddell[28] demonstrated similar endings in the skin subserving cutaneous pain mediation. Feindel, Weddell and Sinclair[26] discussed the free nerve endings of the type demonstrated in tendons and were of the opinion that such endings were responsible for nociceptive responses in animals and sensations of pain in man. The presence of "pain"

endings in muscles and tendons, as well as in the skin, is contrary to the theory developed by Goldscheider[29,30] in which he regarded pain, from either superficial or deep structures, as being mediated by the nerves of "touch," occurring as a result of a central summation of a large number of touch stimuli, that is, "overstimulation" of tactile endings. This theory of Goldscheider was refuted most vigorously by vonFrey[31,32] and at present has little support in regard to cutaneous pain[21,28] and only questionable support for deep pain.[23,27,33,34]

As is well known in the case of cutaneous sensibility, the different modalities are sorted out in the spinal cord and ascend in tracts mediating impulses set up by like stimuli. Such is the case with the deep sensibilities. Therefore, a lesion in the central, and not in the peripheral, nervous system is capable of eliminating deep pain without affecting the other deep sensibilities. This is important, not only in clinical diagnosis but also in the surgical elimination of pain, since the deep somatic structures of the body are subject to disease processes and the pain which frequently accompanies such processes.

According to Head and Thompson,[35] impulses set up by painful stimulation of muscles, tendons and joints ascend in the opposite side of the spinal cord, in company with fibers mediating impulses set up by painful stimuli from the skin. However, although their material consisted of thoroughly studied clinical cases of partial spinal cord lesions, the location of the lesions, for the most part, lacked anatomic confirmation. In all three of the monkeys used in the present study, there was a loss of deep pain only on the side opposite the spinal cord lesion and below it, and the limits of the various spinal cord lesions were confirmed anatomically.

Because of the possibility of deep pain arising from "overstimulation" of positional sense nerve endings,[23,29,30] it was thought desirable to rule out possible conduction, within the dorsal white column, of impulses set up by deep pain stimuli. Another indication for the need of such investigation of the functions of the dorsal white column is apparent, when it is recalled that Foerster[36,37] was able to obtain definite pain when fasciculus gracilis was touched in the cervical region, although paresthesias were the rule. Following section of the dorsal white column on the right side in monkey No. 33, there was still an appreciation of deep pain which was of equal and like quality from both lower extremities. Therefore, impulses set up by deep painful stimuli do not ascend exclusively in the dorsal white column of the cord on the side of their origin to conscious levels, as do those related to an awareness of the position of the parts of the body. It seems unlikely that "overstimulation" of a peripheral ending would cause impulses in the central nervous system to seek entirely new ascending fiber pathways. This information, combined with that obtained from the monkeys (No. 31 and No. 32) with ventrolateral cordotomies and no dorsal white column section, proves that no impulses from tendons that are interpreted as pain ascend in the dorsal columns in the monkey.

Since section of only the ventrolateral region of the spinal cord (monkeys No. 31 and No. 32), with interruption of fibers mainly of the lateral spinothalamic, spinotectal and ventral spinocerebellar tracts, interferes with both cutaneous and deep pain conduction, it seems plausible to assume that impulses set up by deep painful stimuli accompany those aroused by cutaneous painful stimuli in the lateral spinothalamic tract. That such is the case has been confirmed clinically by studies on the spinal cord by Peet,[38] Lewis,[19] Kellgren,[39] Kahn and Rand[40] and others and, for the midbrain, by Walker.[41]

It is well known that there is a pattern of topographic localization in the lateral spinothalamic tract[37,38,42,43] and such a pattern has been accurately worked out recently by surgical[1,44] and anatomical means.[2,3,4] The above localization has been assigned to the lateral spinothalamic tract fibers mediating impulses set up by painful stimuli from the superficial areas of the body. This pattern is shown in figure 3 with fibers arising from the most caudal region of the spinal cord shifting, as they ascend, to the most dorsolateral portion of the tract and the short fibers, arising from cephalic regions of the cord, located in the more ventromedial portion of the system. The question arises whether there is likewise such a pattern for deep somatic pain. In monkey No. 31 deep pain from the lower extremity was eliminated by section of the most dorsolateral part of the contralateral lateral spinothalamic tract and deep pain was preserved in the upper extremity on the side opposite the partially sectioned lateral spinothalamic system, indicating that the uninterrupted ventromedial portion of the tract mediated impulses set up by deep painful stimuli arising in the upper extremity. This implies that deep pain is carried in the lateral spinothalamic tract in accordance with the same localization pattern as superficial pain. Kahn and Rand[40] have presented clinical material which indicates that both deep and superficial pain from the lower extremity is mediated in the most dorsolateral fibers of the lateral spinothalamic tract on the opposite side. Therefore, deep pain in both monkey and man accompanies superficial pain with a similar pattern of localization for both in the lateral spinothalamic system. A schematic representation of the pathways for impulses set up by painful stimuli from both the skin and the tendons is shown in figure 3.

Does deep pain reach consciousness at subcortical levels? The indications are that it does so. For example, in monkey No. 31 deep pain from the upper extremity was found to be unaltered following a large cortical lesion in the contralateral sensory upper extremity area (figure 2). This is consistent with the findings of Head[10] and others for clinical cases, in which superficial pain was still present following cortical lesions. Presumably the dorsal thalamus is the anatomic site in which deep pain reaches conscious levels, although the optic tectum or other cortical areas cannot be excluded.

Before concluding the discussion, the author would like to point out that there is a definite need of more accurate knowledge of the peripheral distribution of the related nerves and the central course of fiber systems carrying

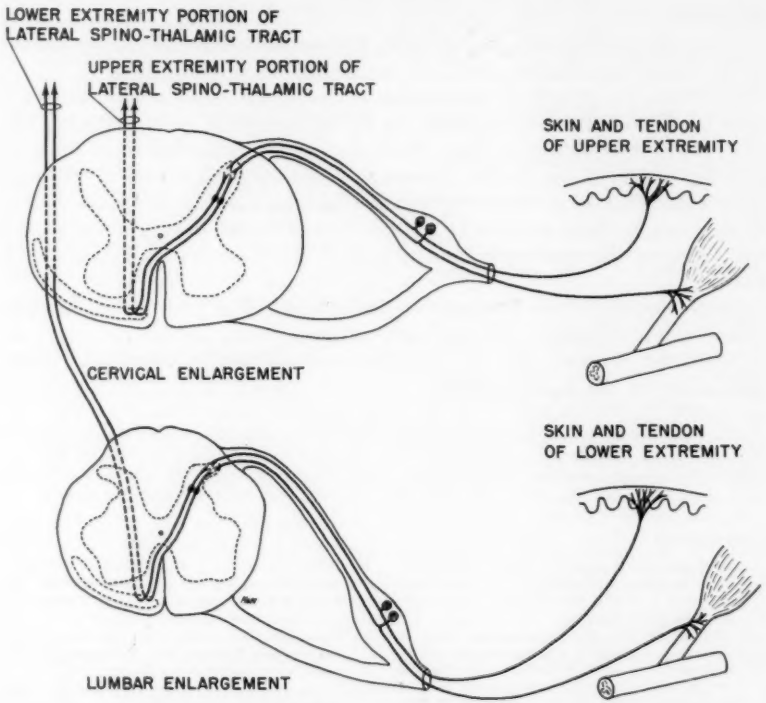

FIG. 3. A diagrammatic representation of the writer's conception of the connections within both the peripheral and central nervous system concerned with impulses set up by superficial and deep painful stimuli.

impulses set up by painful stimuli within the deep somatic tissues of the face region. Some of the cases of atypical facial neuralgia present many characteristics of deep somatic pain and a further study of deep pain, especially in the facial region, may aid in clarifying a difficult problem for the neurosurgeon in his attempts to relieve facial pain surgically. The indications are that pain fibers from the face region are present in nerves other than the trigeminal since complete section of one trigeminal root may not relieve facial pain on the side of the rhizotomy.[47] Studies by Walker,[46] Jackson and Ironside,[47] and Erskine and Rowbotham[48] indicate that the central and the peripheral connections[49] underlying such atypical neuralgias are not the same as those providing pathways for painful stimuli set up in the superficial face region. Further study of both peripheral and central pathways mediating impulses set up by deep painful stimuli, especially in the facial area, should be very fruitful.

SUMMARY

1. In the monkey, impulses set up by painful stimulation of tendons ascend in the lateral spinothalamic tract on the side opposite their origin.

2. There is a pattern of localization in the lateral spinothalamic tract not only for fibers mediating impulses set up by superficial painful stimuli but also for fibers carrying impulses from the painful stimulation of tendons. Impulses set up in the Achilles tendon by painful stimuli ascend in the most dorsolateral portion of the lateral spinothalamic tract on the side contralateral to their origin; those aroused by painful stimuli in the wrist tendons ascend over fibers in the more ventromedial part of this contralateral spinothalamic bundle.

3. No impulses from tendons that are interpreted as pain by the monkey ascend in the homolateral dorsal white column.

4. In the monkey, deep pain reaches consciousness at subcortical levels, presumably in the dorsal thalamus.

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The abnormal action of the nerve centre, by which the phenomena are immediately produced, may be conveniently spoken of (following the example of Hughlings Jackson) as a "discharge." The word is thus employed merely as a designation for the sudden violent functional activity of nerve cells, causing the spasm which the observer sees, or the sensation of which the patient is conscious. Thus used it involves no theory of the nature of the process which goes on in the nerve cell. It merely designates that which no one can deny, the sudden liberation of energy somewhere in the nerve centres. The energy liberated is what we call "nerve force," which may excite another liberation of energy in the muscles, as visible spasm. The liberated nerve force is thus recognized by another person solely by its effects, but it may directly affect the consciousness of the individual. Hence the study of the subjective modes of onset of fits, the warnings of which the patient is conscious, is of great importance and full of promise of additions to our knowledge of the intimate pathology of the disease.

— W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Aphasic Difficulties Understanding Spoken Language

Hildred Schuell, Ph.D.

It is now generally recognized that in aphasia there is impairment of more than one language function and that partial as well as total losses occur in all language areas. Therefore it is to be expected that although most aphasic patients have difficulty understanding spoken language, some understanding is usually retained. This is in agreement with clinical findings. Sometimes, under certain conditions, the patient understands what is said; sometimes he does not. The degree and severity of involvement vary from patient to patient.

Superficial and limited observations of the patient's behavior may be misleading. The response of the patient to context, to one or two words in a sentence, or to a situation may be such that he appears to understand all that is said, though this is far from the true condition. Actually, it is impossible to evaluate receptive involvement without systematic examination.

It appears, from working with a large number of aphasic patients, that there is a correlation between the type of impairment affecting comprehension of spoken language and the amount of improvement accomplished by therapy. This correlation depends less upon the degree of impairment than upon the specific kind of receptive difficulty present. Thus it appears that receptive language disturbances do not constitute an entity but that individual components operate selectively in relation to prognosis. Results obtained from the study of 138 aphasic patients have made it possible to divide auditory defects into two general groups. These groups can be identified by simple testing, and prognosis for recovery of speech can be based upon the results.

APHASIC PATIENTS STUDIED

The group of 138 male patients who were studied for language disturbances ranged in age from 19 to 71 years, and included tumor, traumatic and vas-

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cular cases. This group comprised all patients seen in the Aphasia Center of the Minneapolis Veterans Administration Hospital between April 1948 and August 1952 who presented aphasic disturbances and who were observed for a long enough period to make an evaluation of recovery possible. All patients were tested extensively for aphasic disturbances upon admission.

TESTS FOR UNDERSTANDING SPOKEN LANGUAGE

To explore the ability to comprehend spoken language a series of tests was constructed, which ranged in difficulty from understanding single words to grasping the meaning of a complex paragraph. These tests were administered experimentally to both aphasic and nonaphasic patients, and five items were then selected which had proved most successful in testing for aphasic impairment. These items have been revised from time to time in order to secure more specific data. It is not felt, however, that these revisions have influenced the results discussed in this study, since general findings have remained essentially unchanged. The five tests for understanding spoken language now used by the Aphasia Center are as follows:

1. *Understanding single words.* Six common objects – a comb, a cup, a key, a pencil, a penny, and a spoon – are placed in a group before the patient. He is shown that he is to point to the object the examiner names. Next, two groups of pictures are presented, one group at a time, and the same procedure is followed. The first group includes pictures of the following common objects: bed, car, chair, clock, house and table; the second has pictures of these: boy, dog, flower, girl, horse and tree. Lastly, the picture of a man is shown, and the patient is asked to point to the following: ear, eye, foot, hair, hand, mouth, belt, collar, shirt, shoes, tie and trousers.

The test for understanding single words is valid only if the following conditions are fulfilled.

(a) The patient must see and recognize the objects; to ascertain this he may be asked to match duplicate pictures. Also, his ability to use common objects appropriately should be observed.

(b) The patient must understand the task and cooperate with the examiner. If there is any doubt about this, the task should be demonstrated and practiced with a trial group of objects before the actual test is given.

(c) After the patient understands the task, only one word should be spoken. The examiner should say, "comb," and wait for the patient to respond; he should not say, "Show me the comb," or "Point to the comb." Directions such as these, however, may be given in the beginning and repeated when necessary.

2. *Understanding directions.* This item tests the patient's ability to follow directions of progressive length and difficulty, and distinguishes between general impairment of language comprehension and specific disability related to impairment of body scheme.

3. *Recognizing errors.* This item allows the examiner to observe whether the patient grasps the full significance of what is said, or whether he merely responds indiscriminately to a few words he recognizes. The following are examples.

(a) You eat with a knife, fork and comb; is that right?
(b) Many American people own cars; is that right?
(c) Columbus discovered America in 1942; is that right?
(d) Bread, butter and nails are good to eat; is that right?
(e) There are many railroads in the United States; is that right?
(f) If you have a hard time getting up in the morning, you should try going to bed later at night; is that right?

4. *Understanding simple narrative.* This item tests the patient's ability to follow and comprehend a related sequence of statements. The paragraph given below is read to the patient; he is then asked the questions which follow.

Yesterday Tommy Burns, age seven, went to Branch Creek to fish. He took his dog, Prince, with him. The creek was swollen by spring rains. Tommy lost his footing and fell into deep water. He might have drowned, but the dog plunged in after him and towed him to shore.

a) Was Tommy going hunting?
b) Did he get lost?
c) Did he fall in the creek?
d) Did his father rescue him?
e) Did his dog go in after him?

5. *Understanding more complex information.* This item is similar to the previous one, but is a little longer, more detailed, and less concrete.

ANALYSIS OF DATA

On the basis of test-retest data, clinical data, and evaluations made by the clinical staff, an estimate was made of the speech of each patient at the time of his discharge. No attempt was made to distinguish between recovery and relearning. Patients were divided into four groups, according to the following criteria.

Group I (excellent recovery of speech). The patients who were placed in this category were able to talk freely about subjects which interested them, and their speech sounded normal most of the time. Excellent recovery was not construed, however, as being synonymous with total recovery.

Group II (good recovery of speech). Patients in this group were able to talk quite normally in everyday situations, but they either had difficulty in expressing ideas of length or complexity or had a mild residual defect in articulation, such as a distorted *s* sound.

Group III (limited recovery of speech). This group of patients had a sufficient command of language to make their needs and wishes known, though they could do so only in an obviously defective manner. This type of patient might be able to use only single words or short phrases; he might have moderately defective articulation; or he might have frequent difficulty in finding the desired word, and then block or substitute an inappropriate term.

Group IV (no functional speech). Those patients who were judged to have no functional speech either could not make themselves understood or could not initiate speech voluntarily. Many patients in the latter group learned to repeat fluently and to use a few highly overlearned or automatic responses; occasionally they even made appropriate responses of a high order. Since, however, they were not able to express their simplest wants with any consistency, speech had no functional value for them.

Next, the original test record of each patient was reviewed, and the number of patients who made errors on each of the tests for understanding spoken language was ascertained. These data were analyzed for each group of patients in order to determine what the significant differences were between original findings for patients who recovered functional speech and those who did not. The test results for patients in all four groups are summarized in table 1.

TABLE 1
NUMBER AND PERCENTAGE OF PATIENTS WHO MADE ERRORS ON TESTS FOR UNDERSTANDING SPOKEN LANGUAGE

	Understanding single words		*Understanding directions*		*Recognizing errors*		*Understanding simple narrative*		*Understanding more complex material*	
	No.	*Pct.*	*No.*	*Pct.*	*No.*	*Pct.*	*No.*	*Pct.*	*No.*	*Pct.*
Group I.–35 patients with excellent recovery of speech (25 per cent of total group)	0	0	14	40	13	37	14	40	35	100
Group II.–47 patients with good recovery of speech (34 per cent of total group)	0	0	17	36	20	43	24	51	45*	96
Group III.–25 patients with limited recovery of speech (18 per cent of total group)	4	16	21	84	19	76	23	92	25	100
Group of 107 patients who recovered speech (77 per cent of total group)	4	3	52	49	52	49	61	57	105*	98
Group IV.–(31 patients who failed to recover functional speech (23 per cent of total group)	31	100	31	100	31	100	31	100	31	100
Total–138 patients	35	26	84	61	83	60	92	67	136*	99

*The fact that two patients made no errors on this item can probably be explained on the basis of an artifact of the test item on one revision, which was soon noticed and revised.

The most significant results appear to be the following: (1) The 31 patients who did not achieve functional speech made errors on item 1 – the test for understanding the meaning of single words. (2) Only four of the 107 patients who recovered functional speech made errors on this item when originally tested. All four of these patients were in Group III, the group comprising those with limited recovery possibilities.

The limited recovery of speech by these four patients can be explained on the basis of spontaneous recovery. Two of them were examined post-surgically – one after the removal of a traumatic left temporal hematoma, and the other after the partial removal of a glioma deep in the left temporal lobe. The other two patients had sustained cerebral emboli. At first the

condition of both patients remained relatively stationary, but after several months they began to show generalized improvement. The gains were slight, however, and serious permanent limitations remained for all these patients.

According to these data the first item in the tests is the critical one. The conclusion can thus be made that the most significant factor in prognosis is the patient's ability to understand single words.

DISCUSSION

Auditory verbal agnosia. The inability to recognize the meaning of spoken words has been discussed in the literature as "word deafness," [1] "auditory imperception," [2] and "auditory verbal agnosia." [3] Some authors have tried to distinguish between the inability to recognize the sound and the inability to recognize the meaning of words. Nielsen,[3] for example, quotes Mills' description of types of verbal deafness: "(1) The patient recognizes the voice as a voice, but nothing more; (2) he recognizes language as such, but does not recognize what is said; and (3) he hears and can repeat, but does not understand what he says."

Such a definition presents difficulties in that it fails to indicate what methods could be used to determine the presence of these disorders; and it does not make clear whether failure to respond to language stemmed from auditory impairment or from more generalized intellectual deterioration.

Dejerine's definition of agnosia, which Nielsen[3] also cites, appears to be more useful clinically: "Agnosia is a difficulty in recognition. Recognition is the psychological phenomenon which permits us by the use of one or another of our senses to identify an object under observation with an object previously observed, and of which we have registered the memory picture in the form of a mental image." Wallach[4] adds that "the arousal of the pertinent trace (or trace complex) amounts to recognition."

The patients in our group had no trouble either in recognizing objects visually or in using them appropriately. It may be assumed, therefore, that the response to the first test was either a failure of recognition through the modality of hearing, or a failure of the spoken word to arouse the pertinent trace complex. This condition may properly be termed *auditory verbal agnosia,* and may be defined operationally as follows: impairment of the subject's ability to select a familiar object, named verbally, from a group of objects, provided that the subject understands what is desired, cooperates in the task, and recognizes objects through other modalities.

It should be emphasized that such an impairment, rather than being an isolated disability, will be accompanied by defects in other language functions. Nor will the impairment be total in most cases. Some words will be recognized, while others will not, and individual items will reveal inconsistencies. Our findings indicate that the percentage of errors tends to remain relatively constant or else decreases gradually during therapy without altering the original prognosis. What this means in terms of testing for auditory

verbal agnosia is that (1) results will not be dependable unless the number of items used is large enough to give a reliable sample of the patient's performance, and (2) the ability to perform the task does not necessarily indicate favorable prognosis if the patient has previously received intensive auditory stimulation.

Even though these findings require that a cautious interpretation be made, there still seems to be enough evidence to indicate that auditory verbal agnosia, as here defined, represents a breakdown of the association processes essential to the basic symbolic functions of language. It may also be assumed that prognosis must be guarded when this disability is present.

Reauditorization. Of the 107 patients who recovered speech, there were 103 who, though they made no errors in recognizing single words, revealed impairment by their performance in the other tests for understanding spoken language. It is necessary to determine why these patients, whose receptive processes were unquestionably impaired, showed a significant improvement, whereas patients who failed to understand single words did not. The simplest explanation is, of course, the difference in the extent of damage that has occurred. Such a difference undoubtedly exists, but clinical findings indicate that qualitative as well as quantitative differences must also be considered in order to understand the nature of auditory impairment. For instance, it is important to discover why one patient who scored at the 99th percentile for normal adults on the Ammons Full-Range Vocabulary Scale,[5] a standardized test for understanding single words, still made errors on such simple items as, "Give me the pencil," and "You eat with a knife, fork and comb; is that right?

To explore this problem a careful and detailed study was made of the aphasic problems of 15 patients who, despite their considerable difficulty in comprehending spoken language, understood single words and were making good progress in the speech clinic. The language disturbances of these patients seemed comprehensible if one postulated that they all stemmed from one basic difficulty, namely, an impairment of the ability to recall or evoke auditory patterns of language. This might be termed impairment of reauditorization.

The language disabilities of these 15 patients showed the following common findings.

1. None of the patients made errors on the test for understanding single words, but all made errors in following simple directions, in recognizing errors, and in understanding the simple as well as the more complex paragraph.

2. All made severe but inconsistent articulatory errors, although none had primary involvement of speech musculature. Gross movements were performed easily and at a normal rate. Two patients produced only jargon at first, though some intelligible speech soon appeared. Verbal output increased rapidly for all 15 patients. This consisted largely of recurring expressions such as, "I know but I can't say it," or, "I'll tell you in just a minute," spoken

normally. On the other hand, attempts to produce specific responses resulted in failure or in defective and labored speech. For example, these responses occurred when the patients named pictures: *sama,* for coffee; *sharving the zavor,* for sharpening the razor; *orsenose man* for snowman; and *duck funting* for duck-hunting.

3. Patients were often enabled to respond or to correct a defective response by being offered a well-established association. For example, a patient who could not name a spoon spoke the word correctly when the examiner suggested, "Knife, fork and ———?" This is a common finding for patients who have trouble recalling words. However, such auditory associations do not usually help dysarthric patients to produce desired movement patterns.

4. The same kind of errors appeared when the patients read aloud. They were inconsistent, and the rest of the sentence was often read correctly.

5. The patients had less trouble in repeating phrases after the examiner than in talking spontaneously or in reading aloud. Although articulation errors simliar to the ones above appeared, they were less frequent when the patient was given the auditory pattern. The number of errors showed a high correlation with the length of phrase, and there were steady and consistent gains in the ability to repeat longer and longer phrases or sentences correctly.

6. All patients could write single words from dictation, but none could write a simple sentence spontaneously or from dictation. They failed on such sentences as, "The sky is blue," and "I have a car," but wrote the same sentences correctly when dictated in two-word rather than four-word units.

7. None of these patients were able to rhyme. Instead, they gave responses like *car – automobile,* and *lake – swim,* tending to associate through meaning rather than through sound. This type of response is also obtained from deaf and hard-of-hearing individuals.

8. All had difficulty in finding specific words.

9. All patients became confused when they tried to express ideas of length or complexity.

10. All patients made steady improvement in (a) articulation, (b) word-finding, (c) reading, (d) expressing ideas orally and in writing, and (e) understanding spoken language, when they received therapy based on intensive auditory stimulation. Articulatory errors disappeared, although no work was done on articulation.

Observation of these patients leads one to conclude that ability to reauditorize is a basic factor underlying not only the ability to understand spoken language but also some of the difficulties that aphasic patients experience in reading, writing, speaking, and formulating ideas.

This does not imply that all the difficulties these patients experienced could be accounted for by impairment of reauditorization. Certainly other kinds of impairment could coexist. On the other hand, it should not be surprising to find apparently diverse symptoms related in some such manner. Speech is an exceedingly complex process, and it is extremely doubtful that

impairment of one major process should not affect other processes and modalities at this level of integration. Hughlings Jackson[6] considered that nervous arrangements underlying speech were largely acoustico-motor arrangements. If this is true, temporal lobe impairment should be expected to produce not an isolated symptom but symptom-complexes of this kind; in addition, extensive testing of aphasic patients with careful description and analysis of results should be expected to reveal such relationships.

Testing for impairment of reauditorization presents more difficulties than testing for auditory verbal agnosia. This condition, it appears, can easily be obscured by other disabilities. However, it should be suspected whenever a patient is found who understands the meaning of single words, but makes errors on other tests for understanding spoken language. Other indications are:

1. The ability to follow a single direction, but not two or more directions given in immediate sequence.
2. The ability to write single words to dictation, but not longer units. (This test cannot be used if other writing disabilities are present.)
3. The ability to repeat short words or phrases easily, but not longer units.
4. The appearance of inconsistent articulation errors when the patient is required to give specific answers, combined with the emergence of some speech that sounds normal and fluent, though content and vocabulary may be limited.

The best single test for moderate or severe impairment of reauditorization is repetition of words and sentences of increasing length, though it is of no use, of course, if the patient cannot talk. The following items will reveal varying degrees of impairment. The patient is asked to repeat each unit after the examiner, who speaks normally.

a) Snowman
b) Gingerbread
c) Please sit down.
d) Will you answer the telephone?
e) The bus runs every twenty minutes.
f) We live in the third house from the corner.
g) The office is on the twenty-fourth floor of the bank building.

SUMMARY

1. A series of tests for understanding spoken language was administered to 138 aphasic patients. Of 107 patients who recovered functional speech, only four showed initial impairment of ability to recognize names of familiar objects when spoken by the examiner. All of the 31 patients who did not recover functional speech showed impairment on this test when originally examined.

2. It is suggested that impairment of ability to associate a single spoken word with a familiar object be considered auditory verbal agnosia. This disability appears to represent a fundamental breakdown of symbolic processes, and, when present, prognosis is guarded.

3. The evidence also shows that patients may have no verbal agnosia, but still show marked impairment in understanding spoken language. Exploration of the language disabilities of these patients suggests that the basic difficulty is impairment of the ability to evoke or recall sound sequences utilized in language. This condition might tentatively be considered impairment of reauditorization. It appears to be reversible to a considerable degree.

4. Other aphasic symptoms are described which may be secondary to the impairment of reauditorization.

5. It is possible that a relationship may exist between the two kinds of auditory impairment described, but the nature of this relationship is not revealed by the present data.

6. It is not suggested that verbal agnosia and impairment of reauditorization account for all the difficulties which aphasic patients may have in understanding spoken language. There are undoubtedly other contributing factors which merit investigation.

7. The present evidence suggests that terms such as "expressive and receptive aphasia" reflect inadequate concepts of the nature of aphasic impairment, which must be considered in relation to specific clinical findings and their interrelationships.

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A simple test for the relative torpidity of tactile conduction upon the two sides, that I have habitually used, and have not found described by the other authors, consists in touching simultaneously two symmetrical parts and asking which contact was felt soonest. This should be preceded by actual differences in touch, such as these: Right leg first, then left leg simultaneously; then reverse the order in which the sides were touched. Sometimes where the tracts are diseased, and the gray matter of the cord conducts the sensation, the side first touched may be the last to feel it, and a very long interval of delay may occur.

—S. V. Clevenger in *Spinal Concussions*, published in 1889.

Studies in Temperature Regulation

1. Response of Normal Men to Changes in Environmental Temperature

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STUDIES of the effect of spinal cord lesions on certain regulatory mechanisms such as blood pressure, heat regulation, and so forth are being conducted on patients with spinal cord injuries at the Veterans Administration Hospital at Hines, Illinois. In order to determine what particular phases of temperature regulation should be studied in these patients, a preliminary investigation was conducted on healthy human male subjects at Wesley Memorial Hospital and Northwestern University Medical School. The results of this preliminary study are presented in this paper.

METHOD

Seven healthy male subjects, comprising a group of medical and law students from the ages of 22 to 28, were immersed on different days in hot (102° F.), cold (65° F.), and tepid (93° F.) water in a constant temperature, continuous flow tub bath. The time of immersion was 45 minutes in the hot and tepid water and 30 minutes in the cold water. The 30-minute period was used in the case of the cold water experiments because of the extreme discomfort which the subjects felt at the end of that time.

Each subject was immersed on different days to the level of the axilla, xiphoid, and umbilicus in the hot and cold water and the axilla only in the tepid water. These levels were chosen to represent high, middle and lower dorsal segmental levels of innervation by the spinal cord, the first level to be compared with results of lesions of the cervical spinal cord and the other two

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levels with lesions of the thoracic spinal cord. By measuring the water displacement of each subject's entire body and comparing this water displacement when the body was immersed to the axilla, xiphoid, and umbilicus, the per cent of body volume was determined for each level of immersion. These levels represented 80, 60 and 50 per cent of the total body volume, respectively. The total body surface area as well as its fractions represented below the axillary, xiphoid, and umbilical levels was measured in one subject according to the method of DuBois.[10] The per cent of the body surface area so determined corresponded closely to the per cent of body volume. Water was chosen as the medium of temperature changes for the submerged segment of the body so that the skin of the submerged segment would be eliminated as a heat dissipating organ. The resulting state was then comparable to that with absence of heat sweating in a patient with a severely injured spinal cord.

The temperature of the water bath and of the air of the room, as well as the humidity, was recorded before immersion in the bath and at five-minute intervals during the period of immersion. The temperature of the water remained constant for the cold and tepid baths. Only six of the 21 hot water baths varied in temperature; of these, two varied within 0.4, three within 0.5, and one within 0.9 of a Fahrenheit degree. The temperature of the room usually rose one or two Fahrenheit degrees in all of the experiments. In none of the experiments did the temperature fall below the reading recorded at the beginning of the experiment. The relative humidity of the air of the room remained reasonably constant for the duration of each experiment, the variation being on the average plus or minus 3 per cent in both the hot and cold immersion experiments. In practically all instances humidity was higher at the end than at the beginning of the experiment.

The temperature of the subject's mouth and rectum was taken with calibrated clinical thermometers and that of the face and hands with a thermocouple. These temperatures as well as the pulse, respiration and blood pressure were taken before immersion in the bath and at five-minute intervals during the period of immersion. The subjects were also observed during the period of immersion for shivering, pilomotor and sweating responses, and subjective sensations. During the period of immersion the subjects wore a standard sweat shirt with long sleeves. The bottom of the shirt was adjusted to reach the surface of the water.

The t ratios and their significant levels were calculated for the difference of temperature of the mouth, rectum and skin of the face and extremities, as well as the change in pulse rate before and after immersion (table 1). A t ratio of 2.45 with six degrees of freedom is significant at the 0.05 level of confidence. A t ratio of 3.71 with six degrees of freedom is significant at the 0.01 level of confidence. With three degrees of freedom the t ratio has to be 3.18 for the significance at the 0.05 level and 5.84 for significance at the 0.01 level of confidence.

Two successive basal metabolic determinations were made immediately before and after immersion using the Jones Waterless Motor Basal Apparatus.

Heat production was determined from the rate of oxygen consumption and the use of the factor of 4.825 as the caloric equivalent of one liter of oxygen. Heat storage was determined for the period of immersion from the product of the mean change in oral temperature in centigrade degrees and 0.83, which is the factor for the specific heat of tissue, and the mean body weight in kilograms. Heat loss, though equal to heat production under normal conditions, becomes equal to the difference in heat production and heat storage during change in body temperature, and was so determined in these studies.

The subjects were instructed to void and discard their urine two hours before immersion. A urine specimen was collected immediately before and after immersion in the bath for the determination of volume, specific gravity, and pH. Blood samples were obtained immediately before and after immersion for hematologic and chemical study. Red and white blood cell counts were done in duplicate with Bureau of Standard pipettes and hemacytometer. Hemoglobin was determined in duplicate using the Evelyn photoelectric colorimeter. The Wintrobe method was used for the sedimentation rates and hematocrits.

The chemical analyses consisted of total protein and fractions, nonprotein nitrogen, chloride, carbon dioxide combining power, specific gravity, and pH of the blood. A modified Howe's method was used for determination of the total protein and fractions; the globulin was precipitated from the albumin fraction by the technique of Kingsley. The nonprotein nitrogen was determined by the method of Koch and McMeekin, the serum chloride by the method of Wilson and Ball, and the carbon dioxide combining power by Van Slyke and Cullen's method. These methods were used as outlined by one of the authors.[2] The protein and nonprotein nitrogen determinations were done in triplicate and the others in duplicate. Kagen's method[3] was used for the specific gravity of blood; at least three determinations were performed on each sample. The pH of the blood was read directly, using a microelectrode with the Beckman pH meter.

RESULTS

Immersion Studies in Water of 102° F.

Body temperature change. A rise in body temperature was noted in all experiments. The average change in the temperature of seven subjects at the levels of axilla, xiphoid, and umbilicus and the *t* ratios for these variables appear in table 1. The standard deviations from the mean are shown in figure 1. All the differences appear to be statistically significant. The rise of oral temperature was fairly uniform except at the umbilical level of immersion where a fall of an average of 0.25 Fahrenheit degrees was observed after five minutes of immersion, followed by a uniform rise in temperature for the remainder of the experiment. In the case of rectal temperature, there was a sudden rise of about 1.0 Fahrenheit degree at the five-minute period and a gradual rise thereafter. After emerging from the bath, the oral temperature dropped to its pre-immersion level within 20 and 25 minutes in instances of immersion

TABLE 1

DIFFERENCES IN TEMPERATURE AND PULSE RATE BEFORE AND AFTER IMMERSION IN WATER BATH

Level of Immersion	*Water Bath 102° F.*			*Water Bath 65° F.*			*Water Bath 93° F.*		
	*°F.**	*t Ratio*	*P#*	*°F.**	*t Ratio*	*P#*	*°F.**	*t Ratio*	*P()*
				ORAL					
Axilla	1.66	12.0	0.001	−0.52	3.2	0.02	0.15	1.6	0.30
Xiphoid	1.27	6.70	0.001	0.01	0.61	0.60			
Umbilicus	0.75	2.53	0.05	0.71	3	0.05			
				RECTAL					
Axilla	1.81	18.90	0.001	−0.11	0.47	0.70	0.0	0.4	0.70
Xiphoid	1.76	36.0	0.001	−0.71	2.3	0.06			
Umbilicus	1.54	4.50	0.001	0	0	1.00			
				FACE					
Axilla	3.43	7.90	0.001	1.79	3.8	0.01	2.35	1.55	0.30
Xiphoid	3.71	10.80	0.001	1.85	4	0.01			
Umbilicus	3.50	3.04	0.05	2.43	7.6	0.001			
				EXTREMITIES					
Axilla	6.85	6.90	0.001	0.5	2.14	0.10	−0.9	0.75	0.50
Xiphoid	5.79	9.30	0.001	1.28	1.47	0.20			
Umbilicus	4.29	7.50	0.001	1.22	1.0	0.40			
				PULSE RATE DIFFERENCE					
Axilla	20	3.42	0.02	−3	0.29	0.80	−6	6.77	0.01
Xiphoid	17	2.95	0.05	−12	1.86	0.20			
Umbilicus	18	2.76	0.05	−4	1.18	0.30			

*Temperature difference in Fahrenheit degrees.
Significance level at 6° of freedom.
() Significance level at 3° of freedom.
(−) Indication of fall in temperature.

to the umbilical and xiphoid levels, respectively. Although it continued to drop, the temperature did not reach its pre-immersion level at the end of 25 minutes at the axillary level of immersion.

Heat exchange. Following immersion, the rate of oxygen consumption and heat production increased only slightly, though the increase in the rate of heat storage and the diminution in heat loss was more marked, as shown in table 2 and figure 2. The per cent changes from the pre-immersion value in the rates of average heat production, heat loss, and heat storage were as follows: the rate of heat production increased by 10.6, 8.7, and 4.9 per cent; the rate of heat loss diminished by 36.5, 35.7, and 29.5 per cent; that of heat storage increased by 52.9, 48, and 39.5 per cent for the axillary, xiphoid, and umbilical levels of immersion, respectively.

A comparison of the average rates of heat loss and heat storage with heat production for the seven subjects revealed that heat loss was 57.5, 59.2, and 67.2 per cent, while heat storage was 42.5, 40.8, and 32.8 per cent of heat production, for the axillary, xiphoid, and umbilical levels of immersion, respectively.

Pulse rate. A continuous rise in the pulse rate was observed in all levels of immersion, although at the level of the xiphoid and umbilicus there was an initial drop within the first five minutes, then a continuous rise, as shown in

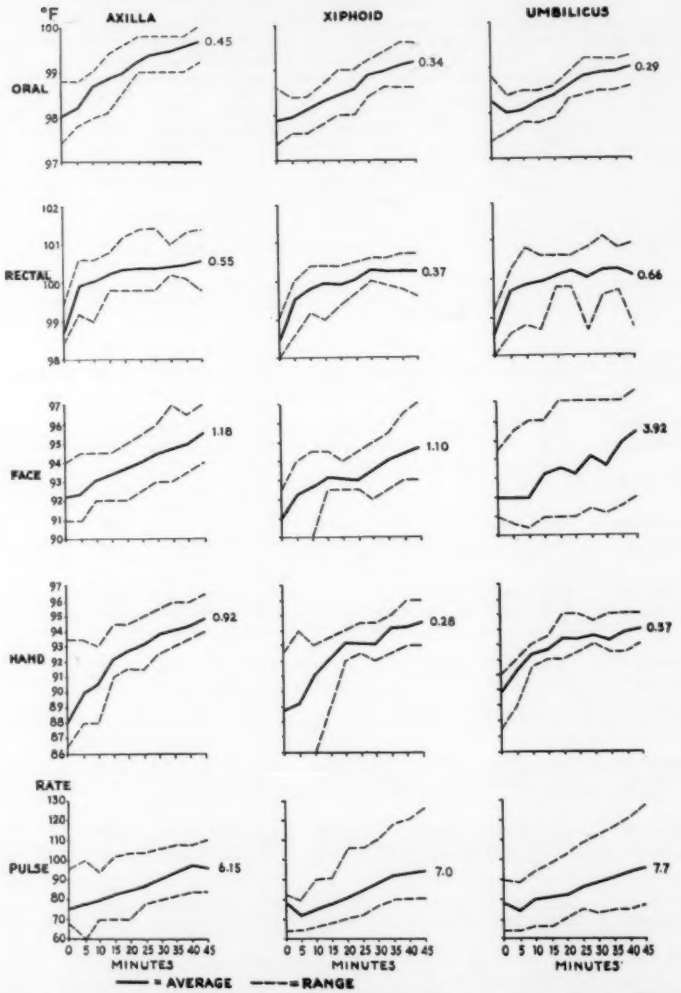

FIG. 1. Temperature and pulse rate curves for period of immersion in water of 102° F. The number at the extreme right of each average curve represents the standard deviation for that curve.

figure 1. The average increase in the pulse rate at the end of the experiment was 20, 17, and 18 pulsations per minute for the axilliary, xiphoid, and umbilical levels of immersion, respectively. These are considered to be statistically significant, as shown in table 1. Bazett[4] reported an increase in pulse rate proportionately to the rise in body temperature.

TABLE 2

VALUES FOR HEAT EXCHANGE IN SEVEN HEALTHY MALE SUBJECTS BEFORE AND AFTER IMMERSION IN WATER BATHS OF 102°F., AND 65°F., AND 93°F.

	102°F.						65°F.					
Subjects	*Wt. (Kg.)*	*O_2 cons. (l./min.)*	*Heat prod. (Cal./min.)*	*Heat storage (Cal./min.)*	*Heat loss (Cal./min.)*	*B.M.R.*	*Wt. (Kg.)*	*O_2 cons. (l./min.)*	*Heat prod. (Cal./min.)*	*Heat storage (Cal./min.)*	*Heat loss (Cal./min.)*	*B.M.R.*
R. W. (Ht. 182.9 cm.)												
Axilla												
Before immersion	69.7	.2581	1.245	..	1.245	+ 4.5	69.9	.2353	1.135	..	1.135	- 4.5
After immersion	68.8	.3200	1.547	0.831	0.716	+30.0	69.5	.3200	1.547	..	1.547	+29.0
Xiphoid												
Before immersion	70.8	.2286	1.104	..	1.104	- 8.0	70.5	.2581	1.245	..	1.245	+ 4.0
After immersion	69.9	.2667	1.287	0.650	0.637	+ 8.0	70.2	.2667	1.287	0.341	0.946	+ 7.5
Umbilicus												
Before immersion	70.4	.2857	1.379	..	1.379	+15.0	70.4	.2500	1.207	..	1.207	+ 0.5
After immersion	69.8	.2667	1.287	0.349	0.938	+ 8.0	69.8	.2963	1.432	0.050	1.382	+20.0
F. E. (Ht. 178.4 cm.)												
Axilla												
Before immersion	79.6	.2963	1.432	..	1.432	+15.0	78.9	.2667	1.287	..	1.287	+ 4.5
After immersion	78.2	.3077	1.485	0.786	0.699	+20.0	78.9	.2758	1.333	-0.066	1.399	+12.0
Xiphoid												
Before immersion	78.6	.2857	1.379	..	1.379	+12.0	77.0	.3200	1.547	..	1.547	+26.0
After immersion	77.8	.2857	1.379	0.668	0.711	+12.0	77.0	.3200	1.547	..	1.547	+26.0
Umbilicus												
Before immersion	78.6	.2857	1.379	..	1.379	+12.0	79.3	.3200	1.547	..	1.547	+24.0
After immersion	78.0	.2857	1.379	0.610	0.769	+12.0	79.1	.3200	1.547	0.131	1.416	+24.0
C. P. (Ht. 167.0 cm.)												
Axilla												
Before immersion	56.0	.1951	0.942	..	0.942	- 8.0	56.0	.1905	0.919	..	0.919	-10.0
After immersion	54.8	.2053	0.991	0.289	0.702	- 2.0	55.7	.2353	1.135	-0.051	1.186	+12.0
Xiphoid												
Before immersion	56.0	.1860	0.898	..	0.898	-12.3	55.5	.1778	0.858	..	0.858	-16.0
After immersion	55.5	.2000	0.965	0.291	0.674	- 5.0	54.9	.2500	1.207	0.130	1.077	+17.5
Umbilicus												
Before immersion	56.1	.1951	0.942	..	0.942	- 8.0	56.1	.1860	0.898	..	0.898	-12.0
After immersion	55.5	.2000	0.965	0.278	0.687	- 5.0	56.1	.2162	1.044	0.122	0.922	+ 2.5
R. S. (Ht. 192.4 cm.)												
Axilla												
Before immersion	62.3	.2053	0.991	..	0.991	-16.0	62.5	.2162	1.044	..	1.044	-11.5
After immersion	60.5	.2222	1.072	0.240	0.832	- 8.0	61.7	.2500	1.207	-0.469	1.676	+ 2.5
Xiphoid												
Before immersion	61.1	.2000	0.965	..	0.965	-18.0	62.7	.2353	1.135	..	1.135	- 4.0
After immersion	61.1	.2053	0.991	0.239	0.752	-15.0	61.8	.3077	1.485	-0.470	1.955	+24.0
Umbilicus												
Before immersion	61.6	.2053	0.991	..	0.991	-15.0	62.9	.2222	1.072	..	1.072	- 9.0
After immersion	60.8	.2105	1.016	0.161	0.855	-12.0	62.7	.2667	1.287	0.177	1.110	+ 9.0

TABLE 2 (continued)

Subjects	102° F. Wt. (Kg.)	O_2 cons. (l./min.)	Heat prod. (Cal./min.)	Heat storage (Cal./min.)	Heat loss (Cal./min.)	B.M.R.	65° F. Wt. (Kg.)	O_2 cons. (l./min.)	Heat prod. (Cal./min.)	Heat storage (Cal./min.)	Heat loss (Cal./min.)	B.M.R.
J. C. (Ht. 186.1 cm.)												
Axilla												
Before immersion	64.5	.2222	1.072	..	1.072	− 8.0	64.9	.2667	1.287	..	1.287	+10.0
After immersion	65.2	.2424	1.171	0.570	0.601	0.0	64.7	.3200	1.547	−0.538	2.085	+32.0
Xiphoid												
Before immersion	64.7	.2286	1.104	..	1.104	− 5.5	64.5	.2353	1.135	..	1.135	− 2.5
After immersion	64.5	.2667	1.287	0.840	0.447	+10.0	64.4	.2581	1.245	0.118	1.127	+ 7.0
Umbilicus												
Before immersion	64.2	.2581	1.245	..	1.245	+ 7.0	65.3	.2581	1.245	..	1.245	+ 6.5
After immersion	64.1	.2963	1.432	0.547	0.885	+22.5	63.9	.3077	1.485	0.202	1.283	+27.0
C. R. (Ht. 170.8 cm.)												
Axilla												
Before immersion	66.9	.2162	1.044	..	1.044	− 6.0	66.9	.2222	1.072	..	1.072	− 3.5
After immersion	66.1	.2500	1.207	0.460	0.747	+ 9.0	66.9	.2857	1.379	−0.244	1.623	+23.5
Xiphoid												
Before immersion	66.5	.2053	0.991	..	0.991	−11.0	67.3	.2053	0.991	..	0.991	−11.5
After immersion	66.1	.2353	1.135	0.458	0.677	+ 3.0	66.8	.2857	1.379	−0.189	1.568	+24.0
Umbilicus												
Before immersion	66.4	.2162	1.044	..	1.044	− 6.0	66.7	.2162	1.044	..	1.044	− 6.0
After immersion	65.7	.2353	1.135	0.457	0.678	+ 3.0	66.4	.2286	1.104	0.121	0.983	− 0.5
J. H. (Ht. 176.5 cm.)												
Axilla												
Before immersion	74.2	.2758	1.333	..	1.333	+11.5	74.4	.2667	1.287	..	1.287	+ 7.5
After immersion	73.1	.3077	1.485	0.650	0.835	+25.0	73.8	.3077	1.485	..	1.485	+24.0
Xiphoid												
Before immersion	74.1	.2667	1.287	..	1.287	+ 7.5	74.0	.3077	1.485	..	1.485	+20.4
After immersion	73.1	.2758	1.333	0.448	0.885	+12.0	73.6	.2963	1.432	0.232	1.200	+20.0
Umbilicus												
Before immersion	73.8	.2581	1.245	..	1.245	+ 4.0	73.1	.3200	1.547	..	1.547	+30.0
After immersion	72.9	.2963	1.432	0.309	1.123	+20.0	72.7	.3200	1.547	0.257	1.290	+30.0

93° F. Axilla

Subjects	Before immersion Wt. (Kg.)	O_2 cons.	Heat prod. (Cal./min.)	Heat storage (Cal./min.)	Heat loss (Cal./min.)	B.M.R.	After immersion Wt. (Kg.)	O_2 cons.	Heat prod. (Cal./min.)	Heat storage (Cal./min.)	Heat loss (Cal./min.)	B.M.R.
C. P.	56.9	.1951	0.942	..	0.942	− 8.5	56.9	.2053	0.991	0.245	0.746	− 4.0
J. C.	66.5	.2758	1.333	..	1.333	+12.5	66.1	.3077	1.485	−0.156	1.641	+26.0
C. R.	67.5	.2053	0.991	..	0.991	−11.5	67.2	.2353	1.135	0.112	1.023	+ 2.0
J. H.	72.5	.2667	1.287	..	1.287	+ 9.0	72.2	.2857	1.379	0.367	1.012	+17.0

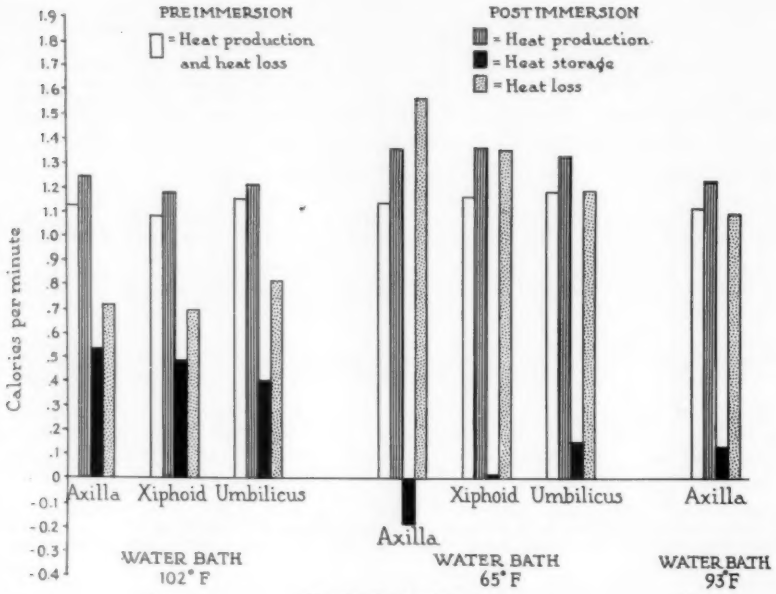

FIG. 2. Heat exchange.

Blood pressure. The blood pressure at the end of the period of immersion was not significantly different from that at the beginning. However, there was a variation during the period of immersion, especially when the subjects were immersed to the axilla. Wakin and coworkers[5] also found the effect of heat on blood pressure was variable. A drop of 8 mm. of mercury in the systolic pressure was noted within the first five minutes of immersion followed by a gradual return to the pre-immersion level. A drop of 10 mm. of mercury in the diastolic pressure was present within the first ten minutes of immersion and remained at this level for the remainder of the experiment. At the xiphoid level the systolic pressure remained unchanged, while the diastolic pressure dropped 9 mm. gradually. At the umbilicus there was an initial drop of 6 mm. in both the systolic and diastolic pressures within the first ten minutes of immersion and then a gradual return to the pre-immersion level.

Respiration. No significant change was observed in the respiratory rate, a rise of one or two respirations per minute being noted in all experiments.

Urine. A slight decrease in the specific gravity and a slight elevation of pH of the urine were noted in all experiments.

Blood. Following immersion there was an increase in the red and white blood cell counts, hemoglobin, hematocrit, specific gravity, total protein, albumin and globulin of the blood. Nonprotein nitrogen was increased at the xiph-

oid and umbilical and diminished at the axillary level of immersion. No change in the sedimentation rate was observed. The blood chloride was slightly elevated at the axillary and xiphoid and diminished at the umbilical level of immersion. The carbon dioxide combining power was diminished at the axillary and increased at the xiphoid and umbilical levels of immersion. No significant change in the pH of the blood was noted, the slight change, when present, being toward the alkaline side. These changes are shown in table 3.

Sweating. When immersed in water of 102° F. at the level of the axilla, the skin of the subjects became flushed, followed by sweating represented first by slight moisture then by small and later by profuse, large beads, the latter state being reached within ten to 15 minutes following immersion. In the case of immersion to the xiphoid level, the appearance of sweat was slightly later and was not as profuse as at the axillary level. At the umbilical level the skin became only moist and sweating did not reach the stage of "beads." The subjects felt considerably fatigued at the end of the experiments, especially when submerged to the level of the axilla.

IMMERSION STUDIES IN WATER OF 65° F.

Body temperature change. The average change in the temperature of seven subjects following immersion in water of 65° F. at the level of the axilla, xiphoid, and umbilicus and the *t* ratios for these variables appear in table 1, while the standard deviations from the mean are shown in figure 3. The oral temperature and the skin temperature of the face appear to be statistically significant, the rectal temperature and skin temperature of the extremities, less so. There was an initial fall, then a rise followed by a gradual fall in the oral temperature at the level of the axillary immersion, while at the xiphoid level an initial fall was followed by a uniform rise up to the 20-minute period of immersion, when a steady fall in temperature again occurred. At the umbilical level there was an initial rise, then a fall of temperature, followed by an elevation thereafter. The rectal temperatures showed an elevation for the first 15 minutes of immersion, followed by a gradual decline of the temperature. The temperature curves of the skin of the face rose uniformly, while those of the extremities showed a fall at the axilla and xiphoid and an alternating rise and fall at the umbilical level. After emerging from the bath, the oral temperature continued to fall, and at the end of 25 minutes the drop averaged one Fahrenheit degree. These results are in accord with those reported from the Dachau concentration camp.[6]

Heat exchange. The rate of oxygen consumption and heat production increased after immersion. At the axillary level of immersion the rate of heat loss was greater than that of heat production, so that the calculated rate of heat storage was a negative quantity. At the xiphoid and umbilical levels of immersion the rate of heat production exceeded that of heat loss. A small rise in the rate of heat storage was noted at the xiphoid and a higher rate at the

TABLE 3

THE MEAN VALUES FOR THE BLOOD DETERMINATIONS IN SEVEN HEALTHY MALE SUBJECTS BEFORE AND AFTER IMMERSION IN WATER BATHS OF 102°F., 65°F., AND 93°F.

	102°F.						*65°F.*						*93°F.*	
	AXILLA		*XIPHOID*		*UMBILICUS*		*AXILLA*		*XIPHOID*		*UMBILICUS*		*AXILLA*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
CO_2 COMBINING POWER (meq/liter)	27.2	27.0	27.2	28.1	27.3	27.4	27.5	29.2	26.7	28.5	25.7	27.0	28.3	29.6
CHLORIDE (meq/liter)	94.8	94.9	95.5	95.5	98.6	97.4	95.2	91.6	95.8	93.3	94.4	91.3	98.5	97.1
pH	7.41	7.42	7.45	7.44	7.46	7.47	7.38	7.32	7.41	7.32	7.42	7.36	7.44	7.40
NON-PROTEIN NITROGEN (mgm./100 ml.)	31.66	31.36	33.34	33.47	30.87	31.41	34.11	34.76	31.9	32.36	33.97	33.71	31.38	30.8
TOTAL PROTEIN (Gm/100 ml.)	6.26	6.64	6.27	6.68	6.27	6.55	6.16	6.75	6.20	6.59	6.21	6.56	6.21	6.41
ALBUMIN (Gm/100 ml.)	4.42	4.83	4.48	4.89	4.23	4.53	4.39	4.99	4.28	4.88	4.39	4.67	4.21	4.63
GLOBULIN (Gm/100 ml.)	1.84	1.84	1.79	1.79	2.02	2.02	1.77	1.75	1.98	1.78	1.82	1.88	2.00	1.77
HEMATOCRIT (in %)	45	47	44	46	44	46	45	49	44	48	45	47	45	47
HEMOGLOBIN (Gm/100 ml.)	14.4	15.4	13.7	14.9	14.1	14.7	14.3	15.6	14.2	15.4	14.2	15.2	14.5	15.2
R B C (million)	4.66	5.16	4.77	5.06	4.82	5.25	4.80	5.22	4.91	5.22	4.84	5.07	4.98	5.36
W B C	5348	5596	5364	6389	5985	6399	5089	6689	5756	6475	5237	5832	5775	5956
SEDIMENTATION RATE (mm)	2.4	3.1	2.3	2.4	1.5	2.0	2.3	2.3	3.4	3.3	2.0	2.3	2.3	2.5
SPECIFIC GRAVITY	1.0582	1.0607	1.0572	1.0599	1.0579	1.0598	1.0582	1.0615	1.0579	1.0615	1.0579	1.0606	1.0584	1.0602

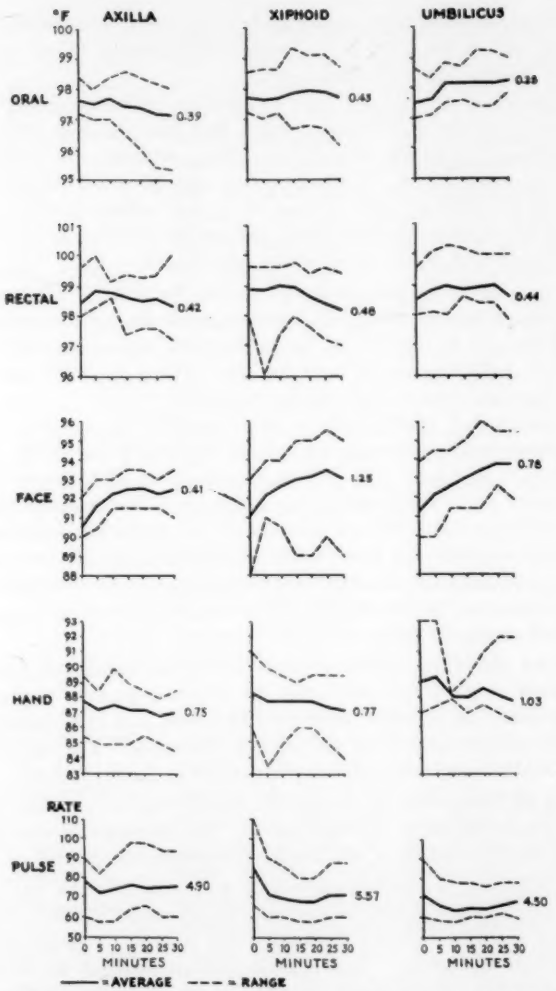

FIG. 3. Temperature and pulse rate curves for period of immersion in water of 65° F. The number at the extreme right of each average curve represents the standard deviation for that curve.

umbilical levels of immersion. These changes are shown in table 2 and figure 2. The per cent change from the pre-immersion value in the average rates of heat production, heat loss, and heat storage was as follows: the rate of heat production increased by 20.1, 17.6, and 11.7 per cent, while the rate of heat loss increased by 37.5, 16.9, and 0.084 per cent for the axillary, xiphoid, and

umbilical levels of immersion, respectively. The rate of heat storage decreased by 19.7 per cent at the level of the axilla and increased by 0.8 and 14.3 per cent at the xiphoid and umbilical levels.

A comparison of the average rates of heat loss and heat storage with heat production for the seven subjects revealed that heat loss was 114.5, 99.4, and 89.6 per cent of heat production at the axillary, xiphoid, and umbilical levels of immersion, respectively. The rate of heat storage was a negative quantity, a minus 14.5 per cent of heat production at the axillary level of immersion. The rate of heat storage at the xiphoid and umbilical levels of immersion was 0.6 and 10.4 per cent of heat production, respectively.

Pulse rate. The pulse rate decreased during the first 15 minutes of immersion and then increased, though it failed to reach the pre-immersion rate, as shown in figure 3. At the end of the experiment the average fall was three, 12, and four pulsations per minute for the axillary, xiphoid, and umbilical levels of immersion, respectively, as shown in table 1.

Blood pressure. A gradual, almost imperceptible rise in both systolic and diastolic pressures was observed, the average rise at the end of the experiment not exceeding 2 or 3 mm. Hg. This is in agreement with Bazett[4] and Kossman.[7] In these cold experiments, especially when immersed to the level of the axilla, it was at times difficult to obtain a blood pressure reading, because of diminished audibility of the sounds coming through the stethoscope. In one subject a blood pressure could not be recorded after ten minutes of immersion in water for the remainder of that one experiment, although his general condition remained good.

Respiratory rate. The respiratory rate showed no significant changes at all levels of immersion. A rise and a fall by as much as four respirations per minute was noted in different subjects. The rises and falls varied in these subjects and had no relation to the level of immersion. The variation in the respiratory rate showed no relation to variations in the pulse rate.

Urine. A slight decrease in the specific gravity and an elevation in the pH of the urine were noted in all experiments. The decrease in specific gravity is in accord with the results of the Dachau concentration camp.[6]

Blood. Following immersion there was an increase in the red and white blood cell counts, hemoglobin, hematocrit, specific gravity, total protein, and albumin. There was a decrease in the globulin fraction. Nonprotein nitrogen was elevated at the axillary and xiphoid and diminished at the umbilical levels of immersion. There was a decrease in the globulin fraction. No significant change in the sedimentation rate was noted, although in some instances there was an elevation by one unit. Blood chloride was diminished, and carbon dioxide combining power increased. No significant change in the pH of the blood was noted, the slight change when present being toward the acid side. These variations are shown in table 3.

Shivering and piloerection. When immersed in water at 65° F. at the axillary and xiphoid levels of immersion, goose flesh appeared within five minutes

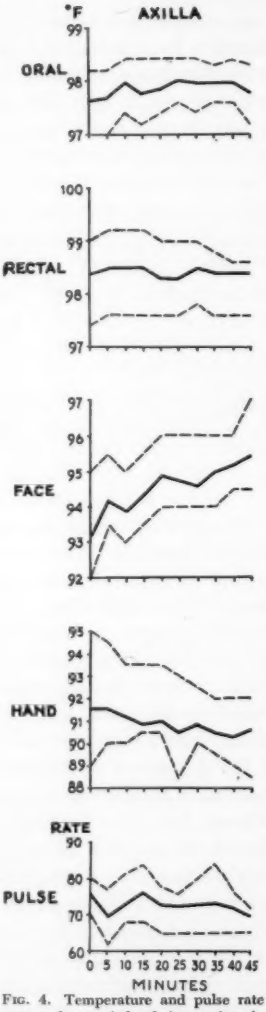

FIG. 4. Temperature and pulse rate curves for period of immersion in water of 93° F. Solid line represents average. Broken line represents range.

and shivering accompanied by gross fasciculation of the muscles within the first ten minutes of immersion. The subjects usually complained of stiffness in the musculature of the lower limbs, which, however, felt soft on palpation. In the case of immersion to the umbilical level, shivering appeared ten or 15 minutes following immersion, and was of much lesser degree than at higher levels of immersion. No fasciculation of the muscles was observed when submerged at the level of the umbilicus. The shivering and sensation of cold, especially following immersion to the level of the axilla and xiphoid, continued for several hours after emerging from the bath and the subjects wore heavy clothing to classrooms to keep warm. The skin of the face became somewhat flushed while that of the hands became pale following immersion in cold water in all the experiments.

IMMERSION STUDIES IN WATER OF 93° F.

Body temperature change. The average change in the temperature of four subjects following immersion in water of 93° F. at the level of the axilla and the *t* ratios for these variables are shown in table 1 and were as follows: the oral temperature increased by 0.15 Fahrenheit degrees, while the rectal temperature showed no change. The skin temperature of the extremities dropped by 0.9 Fahrenheit degrees, while that of the face showed an elevation of 2.35 Fahrenheit degrees. The *t* ratios do not indicate that these changes are significant. The oral temperature curve for the period of immersion was characterized by a discontinuous slow rise while that of the rectal temperature showed hardly any change. A similar curve for the skin temperature of the face showed a uniform rise and that of the extremities a uniform fall. These curves are shown in figure 4.

Heat exchange. There was a mild increase in the rates of oxygen consumption, heat production, and heat storage and a diminution in that of heat loss, as shown in table 2 and figure 2. The per cent changes from the pre-immersion rates of the average heat production, heat loss, and heat storage were as follows: the rate of heat production and heat storage increased by 9.5 and

12.2 per cent, respectively; that of heat loss was diminished by 1.5 per cent. The average rate of heat loss was 90 per cent and that of heat storage 10 per cent of the rate of heat production for the axillary level of immersion.

Pulse rate, blood pressure, and respiration. The pulse rate dropped six pulsations per minute following immersion. The *t* ratio indicates this change to be statistically significant as shown in table 1. No change in the blood pressure or respiratory rate was noted during the period of immersion.

Blood and urine. Following immersion, as shown in table 3, there was an increase in the red and white blood cell counts, hemoglobin, hematocrit, specific gravity, total protein, albumin, and carbon dioxide combining power. There was a fall in the globulin fraction, nonprotein nitrogen, and chloride. No significant change was observed in the sedimentation rate or pH of the blood. No change was noted in the specific gravity and pH of the urine for the period of immersion as compared to the pre-immersion values.

Sweating, piloerection, and shivering. No sweating, piloerection, fasciculation of muscles, or shivering was noted during or following immersion in a water bath of 93° F.

DISCUSSION

The observations noted in these experiments indicate that, when normal men are immersed in a water bath of either 102° F., 65° F., or 93° F., the temperature regulating facilities of the body function best in inverse proportion to the volume or surface area of the body immersed in the bath. The temperature variations from the pre-immersion level were greatest in instances of immersion to the axilla and least in immersions to the level of the umbilicus. At the umbilical level of immersion the temperature curves were characterized by alternating small rises and falls as compared to the axilla, where a reasonably continuous progressive change took place. The rise of the body temperature in the case of immersion in water of 102° F. occurs in the presence of an increase in bodily heat storage and diminution in heat loss and a much lesser increase in heat production, the latter being but a small quantity as compared to the former two. The envelopment of the subject by warm water, with a proportionate diminution in the body surface area exposed to the surrounding air, favors interference with heat loss and facilitation of heat storage. This rise in the rate of heat production with a simultaneous increase in rate of heat storage and decrease in rate of heat loss is presumably related to the increased effort on the part of the heat dissipating facilities to overcome these conditions by promoting surface vasodilation and sweating, associated with an increase in metabolic and heart rates, all observed in the course of the experiment.

The fall in body temperature in the case of immersion in water of 65° F. to the axillary level of immersion occurs in the presence of an increased rate in bodily heat loss and a simultaneous diminution in the rate of heat storage. The effectiveness of a rising rate of heat production is cancelled out by a

correspondingly equal rate of depletion of bodily heat storage, so that the increase in heat production is obviously not of sufficient magnitude to compensate for greater rate of heat loss, which exceeds the former by 14 per cent. In the case of immersion to the level of the xiphoid or umbilicus, the rate of heat production is greater than that of heat loss, so that a reservoir of heat is available to replace heat which is lost. At the xiphoid level the rate of heat production exceeds that of heat loss by 0.6 per cent, while at the umbilicus it exceeds the latter by 10.4 per cent. Therefore, at these two levels the oral temperature shows a rise at the end of the experiment. An insignificant variation in the sedimentation rate was also found by Fetter and Schnabel during and after fever therapy.[8]

The slight rise in body temperature in the case of immersion to the axillary level in a water bath 93° F. occurs in the presence of a diminution in the rate of heat loss and an increase in the rates of heat production and heat storage. The rate of heat production exceeds that of heat loss by 10 per cent for the period of immersion. The elimination of a large surface of the skin area from participating in heat dissipation results in the increased rate of heat stored and a diminished rate of heat lost.

The increases in the rates of oxygen consumption, metabolism, and heat production following immersion were parallel in all experiments. The increases were greater in the case of the cold than in the hot immersion experiments, and were in direct proportion to the volume and surface area of the body submerged. It was only in the immersion to the axilla in the cold water that heat loss exceeded that of heat production. This was also found by Behnke and Yaglow[9] when the subject was immersed to the shoulders. DuBois[10] states that the greater increase in oxygen consumption during the immersion in cold water was probably due to shivering. Wells and Rall,[11] however, showed that shivering is not responsible for increase in oxygen consumption.

The increases in the red and white blood cells, hemoglobin, hematocrit, total protein, albumin, and specific gravity of the blood, both in the hot and cold immersion experiments, are similar to those reported in artificially-induced fever in cabinets[1,12] and in exposure to cold environment.[6,7,13,14] These findings are considered to be related to hemoconcentration.[14,15,16] In instances of immersion in hot water, hemoconcentration results from loss of fluid through sweating. In the case of exposure to cold, the hemoconcentration is secondary to the vasoconstriction in which a transfer of water from the blood vessels to the interstitial spaces takes place without any significant alteration in the total body fluid content. Barbour and coauthors[17] concluded from their work with deep hypothermia that the water moved from the surface of the body to the interior of the cells themselves, and also the increased metabolism in these cells attracted water by osmotic pressure. That vasoconstriction, especially in the vessels of the extremities, is present is supported by the difficulty in obtaining blood pressure readings, a falling in the skin temperature, and in slowing of the pulse rate.

The slight increase in the blood total protein and no change in nonprotein nitrogen after immersion in the cold water agree with the findings in the Dachau concentration camp[6] and the work of Talbott.[18] The increase in carbon dioxide combining power and decrease in chlorides do not agree with the findings at Dachau.[6] However, their subjects were placed in water varying from 2.3° C. to 12° C.

It was noted that in the case of immersion in water of 102° F. the temperature change in all the bodily areas tested was of statistical significance. In the case of immersion in water of 65° F., only the oral and facial skin temperature changes appear to be statistically significant. It is possible that temperature changes involving the whole organism are reflected more readily in the temperature of the mouth and skin of the face than in that of the rectum and skin of the extremities. Vascular changes in the face characterized by pallor or flushing in the course of emotional responses in normal subjects correspond with great regularity to similar changes in the gastric mucosa.[19]

CONCLUSIONS

1. Seven healthy male subjects were immersed on different days in hot (102° F.), cold (65° F.), and tepid (93° F.) water in a constant temperature, continuous flow tub bath to the level of the axilla, xiphoid, and umbilicus.

2. The degree of change in body temperature was directly proportional to the volume and surface area of the body submerged in the bath.

3. The rise in body temperature in water of 102° F. is due to a diminution in the rate of heat loss, an increase in the rate of heat storage, and to a lesser degree to an increase in the rate of heat production.

4. The fall in body temperature in water of 65° F. is due to an increase in the rate of heat loss and a depletion of bodily heat storage.

5. The slight rise in body temperature in water of 93° F. is due to a decrease in the rate of heat loss and an increase in rates of heat storage and heat production.

6. Oxygen consumption is increased more in the cold than in warm environment, which may be explained by the degree of shivering in the cold water. In both instances the increase is directly proportional to the fraction of the body immersed in the bath.

7. The pulse rate increases in warm and decreases in cold water baths.

8. Both systolic and diastolic blood pressures show an initial drop and then a gradual rise returning almost to the pre-immersion level in warm water immersions. A slight, gradual rise in both systolic and diastolic pressures occurs in cold water immersions. No change in the blood pressures was observed in immersions in water baths of 93° F.

9. The increase in blood cells, hemoglobin, hematocrit, total protein, albumin, and specific gravity of the blood, observed in both warm and cold immersion experiments, is believed to be related to the state of relative hemoconcentration, which takes place as a result of fluid loss through sweating in warm

water immersions, and to the vasoconstriction and a shift of fluid from the blood vessels to the interstitial spaces in the case of bodily immersion in cold water.

We gratefully acknowledge the guidance given by Dr. Lewis J. Pollock in pursuing this study.

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After reading Sir C. Locock's paper, I began trying the bromide for cases of megrim, at first for those of a catamenial character, and afterwards for all that presented themselves. On the whole, I should say that the results accord very much with the general experience in the case of epilepsy; in certain proportion of cases the continued use of the remedy has been attended with a considerable reduction in the number and severity of the attacks, while in others there has been no appreciable benefit. I have been unable to observe any difference in this respect between catamenial and other cases. I cannot recall a case which could be fairly characterized as a cure.

—Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Intellectual Functions in Aphasic and Non-aphasic Brain Injured Subjects

Ralph M. Reitan, Ph.D.

THE apparent contradiction in evidence and the differences in theoretical positions of various investigators of the phenomena of aphasia emphasize the great need for differential criteria around which the symptomatology may be more meaningfully grouped. The present paper is concerned with only one aspect of the symptomatology; namely, the nature and degree of intellectual loss.

The relationship of intelligence to aphasia is one that has been debated since Hughlings Jackson's early consideration of the problem. However, in the investigations prior to Marie, changes in intelligence occupied a relatively insignificant position of interest, being generally overshadowed by the desire to relate the location of the lesion to a particular aphasic defect. At present, however, the situation has largely changed as evidenced by Weisenburg and McBide's[1] statement, "The old question of the extent to which aphasia involves a 'defect of intelligence' is of course an integral part of the whole discussion of the nature of aphasia."

Although general agreement in regard to intellectual deficit is present between some writers, areas of disagreement perhaps stand out more clearly. Weisenburg and McBride[1] have commented:

> "The extent to which intelligence may be said to be affected is a moot point. Some investigators have held that intelligence suffers because speech is disturbed while others have held that speech is disturbed because of the intellectual disorder."

While recognizing that aphasic disturbances often also involved motor performances, Head[2] did not feel that general intelligence or memory were primarily affected. He conceived of aphasia as a disorder of symbolic formulation and expression which was represented primarily as a language difficulty. Only insofar as the mechanisms for expression were necessary for general intelligence could the aphasic be considered deficient in this respect. Jackson[3,4] had earlier presented a position with which Head's conclusion in this respect is fairly consistent. He cautioned against assumption that aphasic patients' intellectual impairment is as great as would appear from their language difficulties. Kennedy and Wolf[5] have fairly recently made a strong

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statement to the effect that intellectual impairment or deficiency is probably entirely unrelated to aphasia as such. They say:

> "We believe there is a distinction between intellectual defect and aphasia, that thought is possible without speech or words, that defective speech can exist as something apart from intelligence, ideation, attention, memory, and powers of association. There are many examples to demonstrate the truth of this statement."

These latter writers do not mean to imply that aphasia and organic intellectual impairment are incompatible because, as they point out later in their paper, they often occur together. They say:

> "Although thought processes are frequently affected in aphasics, especially with large lesions, it is no more fitting to regard 'Mind' and speech as one than it is to expect every moron to be aphasic."

Marie[6] was the first to postulate that aphasia invariably represents a defect in general intelligence plus a special language disorder. Goldstein,[7] developing his understanding of the problem together with Gelb, emphasizes his belief that intellectual deficit consisting of impairment in abstraction is frequently found in aphasic patients and postulates this loss as the basis for amnesic aphasia. He distinguishes, however, between impairment of the abstract attitude and damage to the "instrumentalities of speech." In literal and verbal paraphasia he believes these instrumentalities of speech to be damaged with no significant loss in the meaning of words or impairment in the capacity for abstraction. However, he describes subjects with no paraphasia, motor losses, or other speech defects who are unable to name objects, even shortly after the correct name has been given and an attempt made to relate the object with the word. He says:

> "It is not a primary memory defect; it is one expression of impairment of abstract attitude. The patient cannot find the words because he cannot assume the attitude in which they normally appear. Even then, if he is able to find the word which belongs to an object, these words are not normal, they have lost 'meaning' as analysis has revealed."

It is well known that Goldstein believes impairment of the abstract attitude is one of the major consequences of brain injury[8] regardless of the presence of aphasia. Thus he holds to the belief that organic impairment of general intelligence and/or the "instrumentalities of speech" may be responsible for disturbance in speech functions.

Weisenburg and McBride[1] lean to the side of Head in their conclusions regarding intelligence in aphasic patients. They say:

> "Much naturally depends upon the definition of intelligence, but it is clear that aphasia does not involve a 'general intellectual defect' such as Marie postulated in addition to the special defect of language. As the majority of authors since Broca have maintained, the clear-cut aphasic patient does not show a general diminution in intelligence. His intelligence suffers in particular ways . . . Marie was wrong in maintaining that aphasia was in any way a general defect of intelligence, but was right in his belief that other types of mental functioning beyond the language might be affected . . . The extent to which intelligence may be said to be affected varies from case to case; but for aphasic patients as a group it is evident, first, that intelligence suffers in so far as the language processes disturbed are necessary to the carrying out of intelligent behavior, and, second in so far as non-verbal activities

TABLE 1

Means and standard deviations for age in years, education in years, and Wechsler MAS Vocabulary according to diagnostic groups

		Age in Years						Education in Years						Wechsler MAS Vocabulary					
		Aphasics		Non-phasics		Controls		Aphasics		Non-phasics		Controls		Aphasics		Non-phasics		Controls	
Injury	N	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Severe	4	24.50	3.90	24.00	3.94	25.00	5.05	10.50	1.12	11.25	.83	10.75	.83	9.17	.23	11.75	2.68	9.62	1.08
Moderate	9	25.22	4.96	25.56	5.89	25.78	3.59	11.56	2.64	11.44	2.04	11.44	2.21	12.44	2.96	11.00	1.39	11.83	1.31
Mild	5	26.00	5.14	26.20	5.64	25.80	5.91	11.40	1.92	11.80	1.99	11.00	2.83	10.60	2.03	12.00	2.10	11.30	1.33
Total	18	25.28	4.89	25.39	5.57	25.61	4.61	11.28	2.35	11.50	1.94	11.17	2.22	11.32	2.75	11.47	2.03	11.20	2.06

TABLE 2

Number of subjects, mean scores, and standard deviations on Rorschach Test variables for aphasic, non-aphasic, and control subjects

		N	R	W	D	Dd	M	SumC	Z	Tot. C R	Tot. V R	Tot. Y R	F+	F	F—	Tot. F R	P	S	T/R
Aphasic																			
Severe	Mean	4	12.00	2.50	9.25	.25	.50	1.25	9.25	2.00	0	1.00	5.75	.50	2.25	8.50	2.50	0	112.75
	S.D.		6.36	1.80	6.94	.43	.25	.43	5.36	.71	0	1.22	2.04	.86	1.78	4.33	1.80	0	50.82
Moderate	Mean	9	30.89	7.11	18.78	5.00	2.22	2.11	25.33	3.11	.33	2.67	11.89	2.44	7.89	22.22	5.78	5.56	75.57
	S.D.		22.31	5.19	15.35	8.68	2.20	2.02	14.19	2.51	.66	1.94	9.26	6.22	5.57	14.02	2.70	7.69	44.51
Mild	Mean	5	34.20	9.00	21.40	3.80	2.00	4.80	26.90	6.60	.40	1.20	14.00	0	4.80	18.80	5.00	5.60	74.75
	S.D.		42.23	5.22	31.87	7.60	3.03	5.48	26.18	6.95	.49	1.60	16.88	0	6.68	23.64	1.41	7.61	19.81
Total	Mean	18	27.61	6.61	17.39	3.61	1.78	2.67	22.19	3.83	.28	1.89	11.11	1.33	5.78	18.22	4.83	4.33	79.90
	S.D.		22.15	5.22	20.76	7.57	2.35	3.51	18.59	4.45	.56	1.85	11.49	4.56	5.82	18.67	2.57	7.14	45.34
Non-aphasic																			
Severe	Mean	4	23.00	4.50	15.50	3.00	0	2.63	15.63	3.00	.50	1.75	10.00	.50	7.00	17.50	3.50	1.25	59.00
	S.D.		8.09	3.50	6.88	2.24	0	1.02	8.81	1.22	.86	1.30	6.44	.50	2.24	8.08	1.66	1.09	13.88
Moderate	Mean	9	20.67	5.56	13.56	1.56	1.33	3.67	15.94	3.78	1.11	3.11	7.89	.44	3.00	11.33	4.56	1.22	67.32
	S.D.		15.49	6.55	10.06	2.73	.81	5.53	15.11	4.66	2.16	4.05	4.31	.95	2.64	6.76	1.75	1.30	24.42
Mild	Mean	5	31.60	7.20	21.30	3.00	3.00	5.10	32.10	5.00	2.20	3.80	12.40	.20	5.00	17.60	4.80	4.20	76.20
	S.D.		11.94	2.92	8.69	1.84	1.70	1.66	12.30	1.10	.88	1.75	5.33	.22	2.67	7.82	1.32	2.18	34.37
Total	Mean	18	24.22	5.78	16.11	2.28	1.50	3.83	20.36	3.94	1.28	3.00	9.61	.39	4.44	14.44	4.39	2.06	68.33
	S.D.		17.03	5.76	11.92	2.92	2.03	4.38	18.06	3.62	1.91	3.48	6.97	.76	3.72	10.19	2.01	2.70	26.72
Controls																			
	Mean	18	29.97	9.06	18.29	2.61	1.56	4.92	34.28	5.45	2.50	4.84	10.84	1.06	3.50	15.40	6.00	4.06	55.38
	S.D.		17.22	10.15	8.64	4.03	2.48	5.94	36.11	5.59	3.47	5.30	5.99	2.25	2.06	8.41	2.77	3.97	24.78

Legend:

R=Number of responses
W=Number of whole responses
D=Number of major detail responses
Dd=Number of minor detail responses
M=Number of "human movement" responses
SumC=Total of values assigned for use of color
Z=Total of values assigned for organization
Tot. C R=Total number of "color" responses
Tot. V R=Total number of "vista" responses
Tot. Y R=Total number of "surface shading" responses
F+=Number of "good form" responses
F=Number of "form" responses neither "good" nor "poor"
F—=Number of "poor form" responses
Tot. F R=Total number of "form" responses
P=Number of "popular" responses
S=Number of "white space" responses
T/R=Time per response

> are handicapped by changes in mental functioning which extend beyond language processes and are not dependent upon them."

Wepman[9] has recently studied the problem of intellectual loss in 68 aphasic brain-injured subjects. He estimated the pre-traumatic intelligence quotient by scores obtained on the Army General Classification Test and compared these with quotients measured with the Wechsler-Bellevue test of adult intelligence at least six months after injury. In spite of the fact that the majority of authors since Broca have maintained that the aphasic patient does not show a general diminution in intelligence, Wepman found the pre-injury mean intelligence quotient to be 98.5 and post-injury mean quotient of the same subjects to be 70.4, a drop from normal to very nearly a moronic level. In light of the experimental evidence to be presented later in this paper, the writer does not feel that Wepman's results necessarily prove Jackson, Head, Kennedy and Wolf, Weisenburg and McBride, and in fact, the majority of researchers in this area wrong. Wepman's findings will be discussed in more detail later in this paper.

PROBLEM

The problem in the present investigation is to determine the nature of intellectual functions in aphasic patients, or more specifically, to determine whether or not brain injury with aphasia produces greater intellectual impairment than comparable brain injury without aphasia.

CASE MATERIAL

In this study three groups of 18 men each were used. The subjects for each group were matched individually and as closely as possible with respect to chronological age, number of years of formal academic training, and vocabulary as measured by the Wechsler Mental Ability Scale Vocabulary subtest. The results of the matching in terms of means and standard deviations for each group are shown in table 1.

One of the groups consisted of right handed brain-injured subjects with injuries in the left cerebral hemisphere who following injury gave evidence of aphasia apparent to gross observation. No detailed determination of the types of aphasic disorders in the group was made. The second group consisted also of brain-injured subjects, but each of these men had received an injury in the right cerebral hemisphere, were right handed, and gave no post-traumatic evidence of aphasia. The members of the aphasic and non-aphasic groups were individually matched as closely as possible for severity of injury, making use of all neurologic and neurosurgical case history material as well as extended routine and laboratory examinations during hospitalization. The third group was composed of controls, individually matched with the test groups, who had no history or evidence of central nervous system involvement. Matching of the groups with regard to age and education provides a control of these factors and tends to eliminate their significance in giving rise to differences in the test scores of the three groups. Matching of the two groups of brain injured subjects with regard to the severity of injury provides

a basis for estimating the effect of aphasia alone. Upon first glance it might seem that the groups should not have been matched for vocabulary level, since vocabulary impairment might be one of the integral aspects of aphasia. However, Kennedy and Wolf,[5] as well as other writers,[1] have pointed out that the aphasic patient frequently knows the meanings of words even though he is at a loss to communicate the definition. The purpose of this study was not to compare the absolute vocabulary level in the three groups, but rather to attempt to compare basic intellectual functions as expressed through the use of language. Therefore, it was felt desirable to match the vocabulary levels in the three groups.

In administering the vocabulary test to aphasic patients every effort was made to determine whether or not the subject knew the meaning of the words. In some instances, because of the patient's difficulty in communication, the examiner took the liberty of departing from standardized administration procedure to the point of suggesting multiple alternatives of definition. This was felt to be legitimate for two reasons; 1) it appeared to be the only way to avoid unfair penalty to certain of the aphasics, and 2) because the aphasic patients consistently showed decided rejection of the alternatives they considered to be incorrect. As will be seen later in the paper, the emphasis in this study was not upon absolute vocabulary but rather upon the use of language in expression of associations.

The brain injured subjects in the two groups were tested generally from three to six months after injury. An attempt was made to delay testing in instances of particularly severe aphasia until the patient had recovered to the point that his improvement was leveling off. None of the aphasic subjects had received any special training to help them overcome language difficulties.

PROCEDURE

The Rorschach test was administered to each of the subjects individually. The examiner had no information regarding diagnostic classification prior to administering and scoring the tests. The subjects in the two brain injured groups were classified into three subgroups, severe, moderate and mild, in accordance with surgeon's notes, neurologic findings and clinical impressions. Mean scores and standard deviations were calculated for each of the groups and subgroups for a variety of Rorschach test variables. The means of the total groups were compared for the statistical significance of differences by means of Student's t technique,[10] except for the subgroup means which were not treated in this manner because of the small number of subjects. As another method of comparing the performance of the three groups, chi-square tests were made of the differences in the frequency with which scores of individuals in one group exceeded scores of matched individuals in the other groups for each of the Rorschach variables used. Finally, the frequency differences between the groups in occurrence of Rorschach test "signs" of brain injury were compared by use of chi-square.

RESULTS

Table 2 presents the number of cases, mean scores, and standard deviations for each group and subgroup for the selected Rorschach test variables.

It will be noted by inspection that generally the means for the brain-injured groups and the controls do not differ greatly. It should be mentioned that an effort was made by the examiner to assist aphasic subjects in expressing their associations when necessary. Retrospective scrutiny of the test protocols of the aphasic subjects reveals that many of them had obvious aphasic difficulties, particularly in the use of nouns. A variety of procedures were devised by these subjects, without the help of the examiner, to overcome the difficulty. Sometimes the problem could be solved by circumlocution, sometimes by pointing, and in some instances the subject either corrected a mistake or gave the correct word initially by persistent effort. Nevertheless, in a number of instances the inquiry period was reached with attempted responses still uncompleted. When this occurred, the examiner encouraged the patient to direct his guessing of the meaning the patient wished to express. The examiner's only function in this respect was to help the patient communicate his own ideas, although no such responses were scored unless the content was clear to the examiner. This procedure was felt to be legitimate with the aphasic patients because it was followed only when the examiner felt certain that the subject had some specific response in mind, and secondly, because the aphasic subjects regularly and emphatically rejected incorrect suggestions. In spite of these procedures, there were still a few unscorable responses in the protocols of the aphasics.

Table 3 presents the *t* ratios comparing the mean Rorschach Test scores for the three groups. The subgroup means were not tested for the statistical significance of differences because of the small numbers.

The *t* ratios in the above table are generally small and indicate that few significant differences are present in the Rorschach test mean scores for the three groups. The non-aphasic brain injured subjects had lower mean scores than did the aphasic subjects on the majority of the measures. Values of 2.90, 2.57, and 2.11 are needed for *t* ratios at the .01, .02, and .05 levels of confidence for groups of the size used in this study. In only one instance does a *t* ratio reach the .05 level in the non-aphasic-aphasic comparisons. It appears at the .05 level of confidence that the non-aphasic subjects give more vista responses than do the aphasic subjects. In comparing the mean scores of the control group with the brain-injured groups and noting those which differ significantly, even more surprising results are found. The controls appear to give more vista responses than the aphasics and also to have shorter response time. The controls differ significantly from the non-aphasics only with respect to the number of "popular" responses given. None of these differences reach the .02 confidence level, but they do exceed the .05 level. Interestingly, among the few significant differences found, none were among the variables traditionally thought of as indicating the level of intelligence or intellectual functioning. The total number of responses (R), the number of whole responses (W), the

TABLE 3

t ratios representing inter-group mean score comparisons for Rorschach Test variables

	R	W	D	Dd	M	SumC	Z	Tot. CR	Tot. VR	Tot. YR	F+	F—	Tot. F	P	S	T/R
Non-aphasics vs. Aphasics	—.59	—.49	—.31	—.73	—.14	.28	—.39	.09	2.27	1.18	—.62	—.84	—.89	—.67	—1.36	—.96
Controls vs. Aphasics	.27	.93	.16	—.46	—.27	1.30	1.24	.89	2.52	2.09	—.09	—1.61	—.58	1.11	—.12	—2.24
Controls vs. Non-aphasics	1.02	1.03	.72	.33	.09	.54	1.23	.81	1.11	1.21	.67	—1.22	.43	2.30	1.57	—1.33

TABLE 4

Chi-square tests of differences in frequency with which scores of individuals in one group exceed scores of matched individuals in other groups

	R	W	D	Dd	M	SumC	Z	Tot. CR	Tot. VR	Tot. YR	F+	F—	F	P	S	T/R
Non-aphasics vs. Aphasics	.53	2.88	.06	.07	.60	3.26	.22	.33	5.44	.07	.06	.22	.25	.60	.07	.53
Controls vs. Aphasics	1.47	.25	2.00	1.66	.50	3.26	.88	1.66	6.24	4.76	.53	.53	.22	.25	2.00	3.56
Controls vs. Non-aphasics	.88	2.00	.88	0	.50	0	.88	.33	.25	.60	.53	.53	0	2.25	2.88	.22

TABLE 5

Chi-square tests of differences in frequency with which Rorschach Test "signs" of brain injury are given in three diagnostic groups

	Rpt	Imp	Plx	AP	Cn	CR	Def	Catas	Inflx	CovCd	Edg	W&R	ActObj	IC	Total Signs
Aphasics vs. Non-aphasics	.176	.110	.110	.120	3.272	0	1.334	.150	.468	1.596	0	.364	4.050	1.596	0
Controls vs. Aphasics	.800	8.862	2.000	.131	.128	11.688	13.486	5.806	8.001	.642	8.690	2.118	1.178	5.806	47.588
Controls vs. Non-aphasics	.232	7.258	3.010	.300	1.124	11.688	7.200	4.500	11.688	.232	8.690	1.028	9.028	2.118	47.588

Legend:

Rpt=Repetition, or the occurrence of similar responses three times in a record without regard for form.
Imp=Impotence, or the recognition of the inadequacy of a response with inability to either improve or withdraw it.
Plx=Perplexity, or the subject's distrust of his own ability with seeking for reassurance from the examiner.
AP=Automatic Phrases, or the use of a stereotyped phrase in an indiscriminate manner in more than half the cards.
Cn=Color naming.
CR=Concrete Responses, or failure to give a single response characterizing a quality or attribute of the object mentioned.
Def=Unclear Definition, or inability to point out clearly the specific details of responses.
Catas=Catastrophic Reaction, or an overt emotional display expressing frustration arising from the test situation.
Infl=Inflexibility, or failure in the entire record to use any part of an ink-blot for more than one association.
CovCd=Covers parts of cards while attempting to formulate associations.
Edg=Edging, or holding the card at unusual angles, peering at it from a side view, etc.
W&R=Withdrawal and Re-attack, or voluntary withdrawal of attention from the ink-blot only to return with new vigor.
ActObj=Consideration of the ink-blots as representative of actual objects.
IC=Irrelevant Comments, or the occurrence of a comment by the patient that is not pertinent to the test situation.

number of human movement responses (M), and probably most important,[11] the Z score (Beck's organizing score)[12] are generally considered the best indicators of intelligence in the Rorschach test. In comparison of the three groups on these variables, none of the *t* ratios were even close to statistical significance. On the basis of the samples used in this study we must propose the absence of significant differences between intellectual functions in these three groups as they are commonly measured by the Rorschach test.

As a further check of the above generally negative results regarding the hypothesis that residual aphasia and/or brain injury without aphasia bring about a significant diminution of quantitatively scored Rorschach test measures, another approach in comparing group performances was followed. The number of individuals in one group whose Rorschach test scores exceeded those for the matched persons in another group were determined for each variable. For example, a frequency tally of the number of controls who had a greater number of responses (R) than their pairs in the aphasic group was made, and vice versa. The significance of frequency differences in the compared groups was then tested by means of chi-square, and are presented in table 4.

The chi-square frequency comparisons above are consistent with the generally insignificant differences in inter-group comparisons found by using the *t* technique. Only a few of the values reach acceptable significance levels. The non-aphasics more frequently give vista responses than the aphasics at the .02 confidence level. The controls exceed the aphasics in two respects, having more vista responses (.02 level) and more surface shading responses (.05 level). Comparison of the controls and non-aphasics show no differences which reach the .05 level of confidence. This approach, then, also reveals no great differences in the quantitative results representing the samples used in this study.

Another procedure used in comparing the Rorschach test results of the three groups shows distinct differentiation of the two brain-injured groups from the controls. Piotrowski[13] and others[14,15] have attempted to propose and evaluate "signs" of brain injury given by the subject during the Rorschach test administration. These signs have been described in the references indicated. Some of them may be obtained directly from the recorded test protocol whereas others of them are based on the individual's behavior during the test administration. Only those signs which Aita, Reitan and Ruth[14] had found to be of value in differentiating posttraumatic brain-injured subjects from controls were used in this study. Table 5 presents the chi-square values representing the statistical significance of the differences in frequency of occurrence of the signs in the three groups.

In comparison of the aphasic and non-aphasic brain-injured subjects, the chi-squares indicate that the Rorschach test signs of brain injury occur with approximately equal frequency. Values of 6.635, 5.412, and 3.841 are needed for significance at the .01, .02, and .05 levels, respectively. Only one of the chi-squares comparing the aphasics and non-aphasics reaches the .05 level. This

sign, "actual objects," refers to the tendency to express associations as if the ink-blots were realistic pictures. The sign was scored only if a record was entirely free from qualifying phrases such as, "Looks like . . ." or "Reminds me of . . .". Interestingly, it was the non-aphasic subjects who showed this sign which is characteristic of brain injury more often than did the aphasics. The total number of signs given by these two groups was exactly equal. Again we have failed to find any substantial differentiation of the two groups of brain-injured subjects.

The comparison of the brain-injured groups with controls reveals, however, definite and consistent differences. Five of the signs occur more frequently, at the .01 level of confidence, among the aphasics than they do among the controls, and an additional two signs reach the .02 level. The non-aphasic brain-injured subjects give six signs more frequently than the controls at the .01 level, and one more sign differs at the .05 level. Thus seven signs occur more frequently at statistically significant levels in each of the brain-injured groups than in the control group. The chi-square values indicate further that the signs which were given more frequently by the aphasic subjects are generally the ones that occurred most frequently among the non-aphasics. Although the Rorschach test signs of brain injury appear to be little influenced by the presence of aphasia as such, the above results reiterate their previously demonstrated value in differentiating between hospitalized controls and post-traumatic brain-injured subjects.

DISCUSSION OF RESULTS

The results of this study reveal no substantial differences between the intellectual functions of subjects with residual aphasia and non-aphasic subjects with comparable brain damage. The differences between the two groups of brain-injured subjects and the controls are indicated primarily by the frequency of Rorschach test "signs" of brain injury. These results would appear to agree with the earlier postulations of Jackson,[3] Weisenberg and McBride,[1] Kennedy and Wolf,[5] and others who have held that the language dysfunction in aphasia is not intimately associated with losses in basic intellectual functions arising from brain injury. Marie and others who have postulated loss in intelligence in aphasia appear to be right only insofar as aphasia implies the damage of cerebral cortical tissue, for in this study no substantial differences were found between the aphasic and non-aphasic brain-injured subjects.

Wepman's[9] finding that a marked loss in intelligence follows brain injury which produces aphasia requires more detailed comment. His results would appear to be consistent with the present findings insofar as the effects of brain damage generally are concerned, but not with regard to increased intellectual impairment in aphasia specifically. Several lines of evidence should be considered in trying to resolve this difficulty. First, Wepman used standard measures of intelligence yielding an intelligence quotient, whereas there is some evidence that the Rorschach test may be more closely related to factors of intelligence which are basic in the sense that they reflect the organic con-

dition of the brain. In a previous study[11] the writer found higly significant relationships between selected Rorschach test variables, including the "signs" of brain damage, and Halstead's[16] measures of biological intelligence. In this same study the relationships between the Rorschach test variables and a test yielding an intelligence quotient were generally insignificant. This would suggest a basis for expected disparity in Wepman's results as compared with the present findings. Secondly, previous studies[17] have indicated that there is no systematic loss in intelligence quotient following brain damage without aphasia. It would appear then that Wepman's findings represent a loss in the quotient specific to aphasia rather than to brain damage generally. The writer has observed several aphasic patients who have obtained very low quotients but who have nevertheless given evidence of approximately normal intelligence when measured by the Rorschach test. In the writer's opinion, substantiated by the demonstrated relationship between the Rorschach test and the measures of biological intelligence, psychometric tests of intelligence are rather heavily loaded with requirements calling for the use of the "instrumentalities of speech" rather than the basic functions of intelligence. It would appear that the Rorschach test, in spite of its visuo-verbal nature, permits the expression of basic factors of intelligence rather than being limited closely by the modality aspects of intelligence. The loss in psychometric intelligence, found by Wepman would seem to be primarily a reflection of the aphasic patient's impairment in modality functions or "instrumentalities of speech" rather than in more basic intellectual functions.

Goldstein's[7] differentiation of impairment of the abstract attitude and loss in "instrumentalities of speech" as bases for aphasia is not substantiated by the findings of this study. The greater frequency of Rorschach test "signs" of brain damage in the two brain-injured groups than in the controls attests to some loss of the abstract attitude as a function of brain damage, but the fact that these signs occurred as frequently in the non-aphasics as in the aphasics gives no evidence of increased impairment of abstraction as a function of aphasia specifically. The strong possibility that these signs of brain damage measure the abstract attitude, at least in part, is supported by their general similarity to symptoms of impaired abstraction as described by Goldstein[8] and by their significant relationship with the Halstead Impairment Index and the abstraction factor of biological intelligence.

SUMMARY

The intellectual functions of three groups of 18 subjects were assessed with the Rorschach test. The groups consisted of brain-injured subjects with residual aphasia, brain-injured subjects with no aphasia, and hospitalized controls. In the three groups, the subjects were individually equated for age, education and vocabulary. The aphasic and non-aphasic brain-injured subjects were equated for the severity of brain damage. In comparing the two brain-injured groups with the controls there was statistically significant evidence of some intellectual impairment, probably related to a loss in abstrac-

tion. However, in comparing the aphasic and non-aphasic brain-injured subjects, no substantial differences were found. The intellectual level of these latter two groups were remarkably similar as measured by the Rorschach test.

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The slight attacks of epilepsy may be characterized by loss of conciousness only. An individual suddenly stops in his occupation, looks strange for a moment, perhaps turns pale, and then goes on with what he is doing, may even finish a sentence which he had commenced, and be aware that something has happened only by finding that he has dropped what was in his hands, or that persons near are looking at him in surprise. The attack is, however, often heralded by some sensory warning or aura, such as precedes the major attacks. It may be accompanied by slight visible spasm, such as putting the arms foreward and bending the head down, or there may be slight convulsion in the part in which the spasm commences in the severe attacks, and, in some cases, the minor attack may be constituted by such spasm, without loss of consciousness. After a slight attack is over, the patient may be quite well. Often he is stupid and dull for a time, and sometimes proceeds to perform some action in a dreamlike, automatic manner, such as undressing himself, retaining afterwards no recollection of what he has done. Sometimes this stage is marked by passion and violence.

—W. R. Gowers in, *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Hydrocephalus With Vascular Malformations of the Brain

A Preliminary Report

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ALTHOUGH a number of authors noticed the existence of hydrocephalus in cases of vascular anomalies of the brain,[2,7,10,11,13,16,17] little attention has been paid to this fact and to its cause in the literature up to now.

In publications concerning this subject three types of abnormalities of the brain are mentioned which may occur with intracranial aneurysms. These are obstructive hydrocephalus, communicating hydrocephalus, and local atrophy of the brain.

Several cases were reported[1,5,6,8,9,15,16] in which the vascular malformation obstructed the aqueduct of Sylvius directly or indirectly by compression of the midbrain or pons, the obstruction being complete or nearly complete. Hydrocephalus was limited in these cases to both lateral and the third ventricles; the fourth ventricle was of normal size and shape. This aspect of the ventricular system was an additional proof for the obstructive nature of the lesion.

Although of rare occurrence, hydrocephalus of proved obstructive character connected with intracranial vascular malformation is not remarkable from the point of view of pathogenesis, as its mechanism is obvious. Much more interesting, and of still not elucidated etiology, is hydrocephalus of the so-called communicating type.

Nevertheless, only a few reports deal with this subject. Olivecrona and Riives[13] have reported general cerebral atrophy in certain cases of arteriovenous aneurysms. Their term "cerebral atrophy" implicates the notion of passive ("ex vacuo") hydrocephalus. This view must be considered as only partially true. In some of our cases with communicating hydrocephalus, as well as in others from the literature,[10,17,18] signs of increased intracranial pressure were registered, pointing to a so-called active hydrocephalus.

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Davidoff and Epstein[7] observed a case of Sturge-Weber syndrome and another of intraventricular venous angioma, associated with moderate dilatation of the whole ventricular system. The ocular fundus was normal. Krayenbühl and Lüthy[10] described two cases of ruptured aneurysm of the circle of Willis with marked internal hydrocephalus. Wyburn-Mason,[18] Verbiest,[17] and Merwarth and Freiman[11] published similar cases. However, most of the authors quote merely the fact that hydrocephalus coexists with vascular malformation of the brain, and only a few[10,11] concern themselves with the possible relationship between those two anomalies.

Local atrophies of the brain connected with vascular anomalies, as described by Olivecrona and Riives,[13] Gösta Norlen,[12] and Bassett,[3] do not belong directly to our subject, which restricts itself rather to the problem of general enlargement of the ventricular system. Local atrophy is generally ascribed to local pressure effect by the vascular malformation or to localized circulatory disturbances.

It is the purpose of this paper to present a series of four cases of arteriovenous aneurysm associated with communicating hydrocephalus, and to discuss the pathogenetic possibilities here involved.

CASE REPORTS

Case 1.—A woman aged 32 suffered from recurrent subarachnoid hemorrhages, the first in 1947, the second in 1948, and the last in 1950. At the time of hospital admission on August 4, 1950, the patient was in semicomatose condition. Neurologic examination disclosed right-sided facial paresis of central type. There were bilateral choked disks, with extensive retinal hemorrhages. Lumbar puncture yielded hemorrhagic cerebrospinal fluid; the pressure was 300 mm.

Because a vascular malformation of the brain was suspected, carotid angiography was carried out on the left side. There was good filling of the internal carotid artery and the posterior communicating artery entered into an arteriovenous malformation in the temporoparietal region (figure 1). This malformation also received branches from the posterior cerebral artery. In the anteroposterior pictures it was clear that the vascular anomaly was situated subcortically. Pneumoencephalographic examination showed a symmetrical ventricular system with markedly enlarged lateral, third and fourth ventricles, and a dilated aqueduct of Sylvius (figure 2).

Case 2.—A man aged 38 had suffered from a subarachnoid hemorrhage in 1941, followed by transient numbness and weakness of his left extremities. Since that time, he experienced occasional mild headaches, particularly when straining. Once in 1948 numbness of the left upper and lower extremities recurred, but subsided after a few days.

About two weeks prior to admission the patient suddenly experienced very severe headaches and nausea while straining at stool and his left side became paralyzed. Later, double vision and stiffness of the neck appeared.

At the time of examination he was fully conscious and cooperative. On neurologic examination a Parinaud's syndrome was found, with miotic pupils which did not react to light. There was also bilateral mild abducens paresis and coarse nystagmus on lateral gaze to both sides. Fundi, visual fields and visual acuity were normal. The left upper and lower extremities were paretic, and there was also a central facial paresis on the left, stiffness of the neck, and a positive Kernig's sign.

Lumbar puncture showed hemorrhagic, xanthochromic cerebrospinal fluid; the pressure was 200 mm.; the total proteins were 140 mg. per 100 cc. The bleeding time, coagulation time and platelet count were normal.

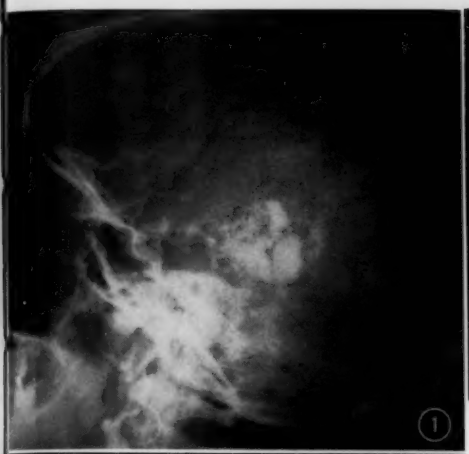

FIG. 1. *Case 1.* Left carotid angiogram. Temporoparietal arteriovenous aneurysm.

FIG. 2. *Case 1.* Pneumoencephalogram: symmetrical hydrocephalus.

FIG. 3. *Case 2.* Right carotid angiogram: arteriovenous aneurysm in the region of the midbrain.

As the history pointed to a possible vascular malformation of the brain, angiography of the right carotid artery was carried out. The anteroposterior and lateral angiograms disclosed an arteriovenous malformation situated in the region of the midbrain (figure 3) to the right of the midline. A pneumoencephalogram showed symmetrical, nondisplaced, rather enlarged lateral and third ventricles. The aqueduct of Sylvius and the fourth ventricle were also dilated without obstruction.

Case 3.—Three weeks before his admission, a 39 year old man collapsed in the street and was admitted to the Municipal Hospital, Tel-Aviv, where he remained unconscious for two days. Some days later he was able to recount that he had suffered headaches and dizziness before the attack.

Neurologic examination disclosed a right-sided spastic hemiplegia and facial paresis of the central type, as well as Parinaud's syndrome. The fundi were normal. There was no sign of blood dyscrasia. Spinal puncture yielded hemorrhagic fluid; the pressure was 250 mm. Plain films of the skull did not disclose pathologic findings.

Left carotid angiography (figure 4) revealed an arteriovenous aneurysm located on the left of the midline in the region of the midbrain. The feeding arteries came partly from the posterior cerebral arteries and partly from the Sylvian vessels; the draining veins were the great vein of Galen and the straight sinus.

Pneumoencephalography was done to rule out the possibility of a highly vascular brain tumor. The whole ventricular system, including the fourth ventricle, was slightly dilated; no sign of any obstruction was noted. The lateral and third ventricles were symmetrical and not displaced (figure 5).

Case 4.—A man aged 39 had had five subarachnoid hemorrhages since 1948, the last in January 1952, when he was admitted to the hospital.

Neurologic examination disclosed no localizing signs. There was stiffness of neck, Kernig's signs, bilateral Babinski, and confusion. Examination of fundus showed bilateral choked disks with massive retinal hemorrhages. Blood pressure was 125/80. The rest of the clinical examination was negative.

On lumbar puncture hemorrhagic cerebrospinal fluid was obtained spurting under an increased pressure of 320 mm. Plain films of the skull were irrelevant. Routine examinations of blood and urine revealed no particular findings.

In absence of any signs indicative for the side of the lesion, carotid angiography was first done on the right. The finding was normal. Left carotid angiography disclosed a paramedian vascular malformation (figure 6), fed apparently by branches of the anterior cerebral artery. In order to rule out a possible, very vascular tumor, ventriculography was performed (figure 7), revealing a high degree of dilatation of the whole ventricular system and aqueduct.

The patient's course proceeded rapidly downhill; he died eventually, being the only one of this series to succumb. At postmortem examination, the brain was cut horizontally, revealing an intricate net of arterial and venous vessels, constituting an arteriovenous malformation within the left lateral ventricle, adjacent to the interventricular wall (figure 8). In addition, there was very marked internal hydrocephalus of the lateral, third and fourth ventricles, with proportional dilatation of the aqueduct of Sylvius. The leptomeninges were milky and thickened and, in the region of the fissure of Sylvius, a brownish color. Histological examination showed the vascular anomaly to consist of thick-walled, distended, large vessels, apparently veins, full of blood. Beneath the ependyma, nodule-like proliferations of glia were noted protruding into the ventricle and sometimes destroying the ventricular ependyma. Some of the ependymal cells had also a yellowish-brown pigment, staining positively for iron.

Various sections of the leptomeninges and of the cortex, taken from different regions of the convexity and of the base, showed that the pia and the arachnoid were extensively fused together. The subarachnoidal spaces disappeared almost completely, particularly over the crests of the gyri. The leptomeninges were also considerably thickened and presented an extensive proliferation of fibroblasts. The pial and arachnoidal vessels were unusually wide and thick-walled. In the fused leptomeninges, many phagocytes with iron pigment were seen. In some areas the meninges contained fresh hemorrhages (figure 9).

Obvious proliferation of the glia was noted in the uppermost layer of the cortex. Numerous microglia cells were found here, containing also much iron pigment (figure 10). No softenings of the cortex were seen. The other layers of the cortex were of more or less normal aspect except for a degree of stasis in the capillaries.

In addition to an angiomatous malformation beneath the ependyma of the left lateral ventricle there was also a chronic adhesive leptomeningeal process leading to obstruction of the subarachnoidal spaces. There were also recent hemorrhages and signs of older ones, that is, hemosiderin-containing macrophages in the meninges and iron-containing microglia cells in the upper layer of the cortex.

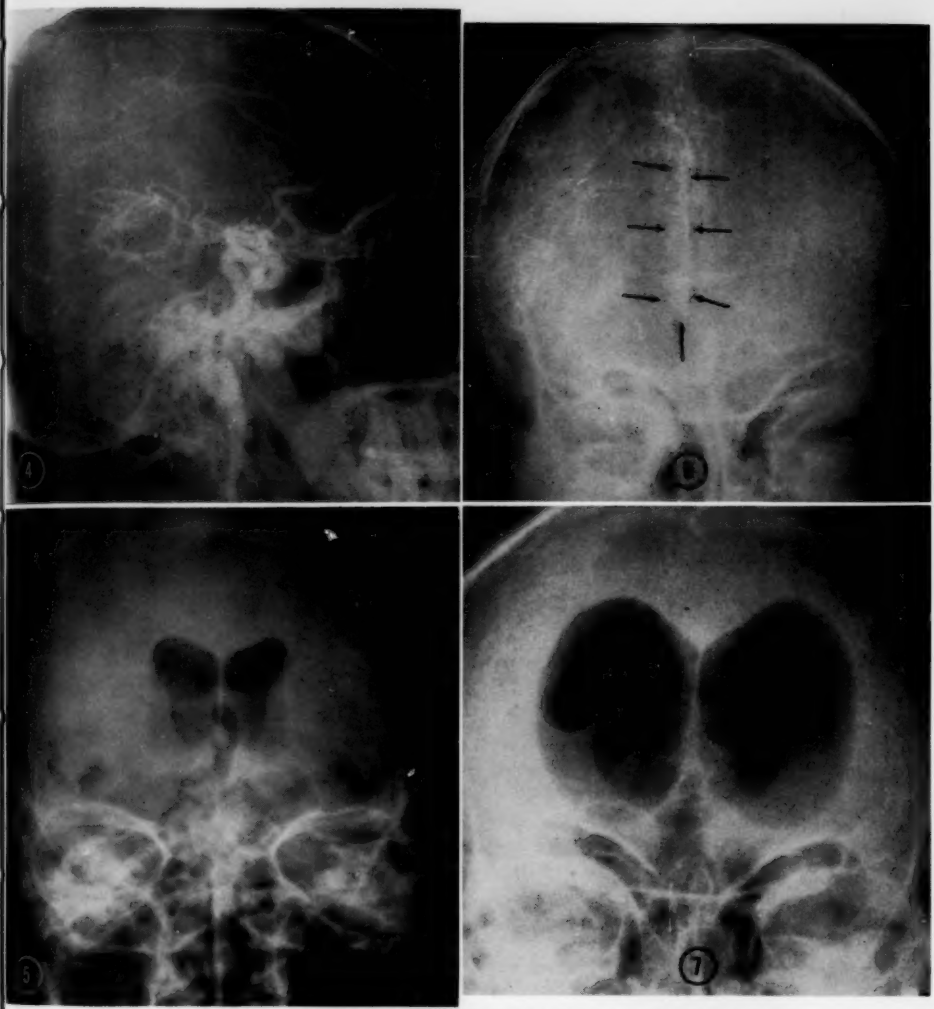

FIG. 4. *Case 3.* Left carotid angiogram: arteriovenous malformation in the region of the midbrain.
FIG. 5. *Case 3.* Pneumoencephalogram: slight symmetrical enlargement of the ventricular system.
FIG. 6. *Case 4.* Left carotid angiogram: paramedian vascular malformation.
FIG. 7. *Case 4.* Ventriculogram: symmetrical, very marked hydrocephalus.

DISCUSSION

In the discussion of the causal relationship between hydrocephalus and intracranial vascular anomalies two problems should be clarified: (1) what causes the hydrocephalus; and (2) is this hydrocephalus active or passive? These points refer to communicating hydrocephalus; obstructive hydrocephalus, whether by direct obstruction, permanent or intermittent, of the aqueduct of Sylvius by intraventricular angiomatous formations[1,9,15] or indirect, by compression of the midbrain,[6,8,16] is not dealt with here.

Concerning the cause of the hydrocephalus, several possibilities have been considered. A few observers[4] were inclined to regard this hydrocephalus as a congenital malformation, a coincident finding in certain cases of cerebral vascular anomalies. However, hydrocephalus occurs too frequently in association with intracranial aneurysm to be considered an accidental finding, and there is experimental, clinical and pathologic proof that some causal relationship exists.

Bagley[2] demonstrated in dogs that hydrocephalus occurs following injection of blood into the cerebral subarachnoid spaces. Detailed microscopic studies of the brain of these dogs showed extensive proliferative reaction of the pia and arachnoid, which led to thickening and adhesion of these membranes. That means an adhesive leptomeningitis and subsequent closure of the subarachnoid spaces was produced. Based on these facts, impairment of cerebrospinal fluid resorption following obstruction of the subarachnoid spaces was assumed; this produced a subsequent accumulation of cerebrospinal fluid and thus hydrocephalus. Further clinical and pathologic studies pointing to this pathogenesis were reported by Merwarth and Freiman[11] and more recently by Krayenbühl and Lüthy.[10] These authors also showed that extensive adhesions and thickening of the pia and arachnoid follow subarachnoid hemorrhage which in turn interferes with the resorption of cerebrospinal fluid, leading to secondary hydrocephalus. An additional fact, supporting this view, is our observation that the greater the number of subarachnoid hemorrhages, the greater the hydrocephalus, as in cases 2 and 4.

But this pathogenesis does not appear probable in all cases; there are instances in which dilatation of the entire ventricular system was noted and which never presented evidence of subarachnoid hemorrhage, as in two patients of Davidoff and Epstein,[7] and case 1 of Verbiest.[17] Other explanations have to be sought.

It seems that the presence of an intracranial vascular abnormality results in a faulty distribution of blood, and subsequently oxygen, to the brain. Secondary atrophy of the brain, following impaired blood supply is likely to occur in such cases. Too little attention has been paid to this problem until the present, and few precise data are available. Verbiest[17] determined the amount of oxygen in the blood of both jugular veins in a small number of patients and found that the amount of oxygen is remarkably higher in the jugular vein homolateral to the vascular malformation. This finding obviously points to the fact that blood entering the aneurysm passes more quickly than it should into the venous system by an arteriovenous shunt, thus depriving the brain of a certain amount of oxygen.

It seems logical that, in some cases at least, a combination of the two mechanisms — faulty cerebrospinal fluid and resorption and impaired blood supply to the brain — might be responsible for the hydrocephalus.

Having reviewed the most important facts concerning the pathogenesis of the hydrocephalus, the question whether it is an active or passive ("ex vacuo")

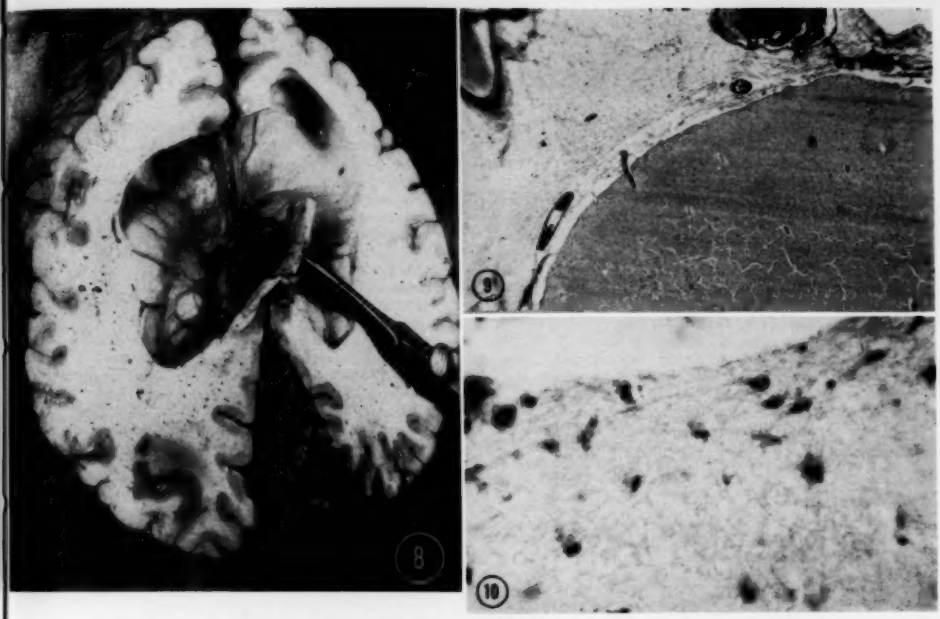

FIG. 8. *Case 4.* The paramedian malformation visible in figure 7 was an arteriovenous aneurysm, adjacent to the medial wall of the left lateral ventricle.
FIG. 9. *Case 4.* Hematoxylin-eosin stain. Thickened leptomeninges, containing fresh hemorrhages.
FIG. 10. *Case 4.* Hematoxylin-eosin stain. Upper layer of cortex, with many microglia cells, containing iron pigment.

process is practically answered; the former is naturally associated with accumulation of cerebrospinal fluid due to impaired resorption, the latter being the sequel of general brain atrophy. Mixed forms might be expected when a combination exists. Further clinical, pathologic and experimental proof is certainly needed before final conclusions can be drawn.

SUMMARY

In a series of arteriovenous aneurysms of the brain, hydrocephalus of the communicating type occurred with regularity. The study of the literature revealed a certain number of similar cases which are reviewed.

Causal relationship between hydrocephalus and vascular anomalies of the brain is stressed, and the most important hypotheses concerning this relatively little known subject are discussed.

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It has been already remarked that in those cases where megrim shows a wellmarked tendency to a regular or periodical recurrence, this periodicity may be disturbed within certain limits, and the accessions in some instances accelerated and in others retarded, by the presence or absence respectively of certain accidental circumstances or bodily states, which act as exciting or determining causes of the seizures.

Where the constitutional predisposition is present in a fully developed form and of a well-marked hereditary type, these accidental circumstances are not at all essential to its manifestation, and the seizures will occur whether they are present or not; but when this is not the case, when the predisposition is originally feeble or latent, and when it is waning or declining in force, the influence of these secondary agencies becomes much more apparent and important, and may make all the difference to the patient between frequent suffering and comparative immunity.

There is, moreover, a great difference exhibited in different cases as regards the nature of the causes which thus determine the seizures, as well as in the degree of their influence; and in some instances at least their operation would seem to depend on an idiosyncrasy of the individual.

Among these exciting causes we may reckon three which seem to have some claim to be regarded as more widely influential than the rest, so far at least as we may judge from the accounts of patients whose inferences are by no means always trustworthy and the generally received opinions in the matter. These are: Gastric disorder, the Catamenial period in women, and Emotional disturbance.

—Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Practical Considerations in the Treatment of Epilepsy

Elinor R. Ives, M.D.

THE GOAL in the treatment of epilepsy is to stop the seizures completely without harming the patient. This takes enthusiasm, wisdom and perseverance on the part of the physician, the patient and research workers.

Control of seizures is accomplished mainly by anticonvulsant medication and the perspicacity of the physician in prescribing it. The physician cannot go by any set formula. He must individualize the treatment in each case. For one thing, different kinds of seizures respond to different drugs. Therefore, the choice of an anticonvulsant will depend on the nature of the patient's attacks. An accurate history should be obtained from eyewitnesses as to what the patient does during the seizures. If the description leaves the doctor in doubt, an electroencephalogram may help in the classification.

It is particularly important to determine if the patient has petit mal. Petit mal is unique in that it is specifically benefited by drugs which are ineffective in, or may even increase, other seizures. In petit mal cases, Tridione or Paradione should be prescribed first, and then trial made of amphetamine, glutamic acid, or of a new compound, P.M. 334 (methyl phenylsuccinimide). However, since these drugs may aggravate other types of seizures, they should be prescribed in conjunction with another anticonvulsant. Patients receiving Tridione or Paradione must be checked for leukopenia at monthly intervals for more than a year.

Psychomotor seizures are more likely to be ameliorated by Dilantin, Mebaral or Mesantoin than by phenobarbital. Many believe that Mesantoin is preferable. Phenurone (phenacemide, phenylacetyl-carbamide) has proved especially valuable in decreasing psychomotor episodes, but unfortunately it is too toxic for general use. When it is prescribed, patients should be closely

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watched for psychotic manifestations, depression of bone marrow and liver damage. Psychomotor seizures have origin in the temporal lobe of the brain. If the patient has incapacitating episodes which cannot be controlled by medication, he should be referred to a neurosurgeon for consultation. In selected cases, removal of certain portions of the temporal lobe may make rehabilitation possible.

Jacksonian seizures have been described as the most refractory to treatment. Drugs which are effective against grand mal commonly reduce the severity of the attacks but may not prevent minor episodes. In these cases brain surgery should be considered. The jacksonian nature of the seizure implies a localized epileptogenic focus. If this is confirmed by the electroencephalogram and if the focus is in an area where surgical extirpation is feasible, a neurosurgeon should be consulted. Angiography may reveal a vascular anomaly, or pneumoencephalography may show posttraumatic adhesions. The most informative neurosurgical procedure is electrical stimulation of the cortex. The area which when stimulated, reproduces the patient's seizures can be excised with the fairly sure assumption that the patient will be helped.

Jacksonian and psychomotor seizures which continue to be incapacitating in spite of strenuous medical treatment should be considered for neurosurgery. These are the only types of seizures in which brain surgery is indicated after a space-occupying lesion has been ruled out.

Grand mal attacks, the typical generalized convulsions, are possibly the most disturbing to the patient but are also the most responsive to therapy. The majority of the anticonvulsants, including phenobarbital, Dilantin, Mebaral, Mesantoin and the bromides, will reduce the severity and frequency of the convulsions. Complete control – eradication of all episodes major and minor – is more difficult.

Choice of anticonvulsant medication depends upon the nature of the attacks and upon the patient's personality. A nervous, apprehensive individual does better with sedative drugs. A lethargic person may do well on medications that are stimulating or at least have a minimum sedative effect. Chronic alcoholics and people suspected of barbiturate addiction should not be given phenobarbital. In treating children it should be remembered that occasionally phenobarbital given to the overanxious mother will help allay the seizures of her small child.

Another factor to be considered in the choice of medication is the patient's previous experience with drugs. The trial and error method is the only way to find the best combination of drugs and dosage. Each of the anticonvulsants has aggravated attacks in some patients and each one has stopped attacks in others. Neither the physician nor the patient is clairvoyant; they must work out control the hard way. The patient must keep an exact record of the occurrence and severity of the seizures. The physician must then translate this record into steppingstones leading to the best possible control.

In the administration of the anticonvulsants certain rules should be followed. When the patient has not had medication previously, it is better to prescribe only one drug – preferably one of the older, safer ones, such as Dilantin or phenobarbital. This should be begun in small doses for adults – Dilantin, 1½ gr., or phenobarbital, ½ gr., after breakfast and supper – then slowly increased until the seizures are controlled or until the maximum tolerated dose is reached. If the patients' tolerance is attained before seizures are stopped, another drug should be prescribed in addition to the

first, beginning with a small dose and gradually building up to the patient's tolerance. If the seizures continue, the newer anticonvulsants should be tried in the same manner; but never should larger amounts be given than are advocated by the pharmaceutical companies dispensing them.

Often a combination of drugs will prove successful when each one alone is only partially so. If, after a fair trial of any medication, the seizures are aggravated or are not appreciably decreased, the drug should be discontinued. It should be remembered, however, that anticonvulsant medication should not be stopped suddenly. Abrupt cessation of a drug, even if another is substituted, may precipitate status epilepticus. The transition from one kind to another should be gradual.

However, if a medicine is toxic to the patient, it must be discontinued immediately. Fatalities have occurred from all anticonvulsants, and the new drugs are more toxic than the old ones. The physician must be on guard. When prescribing new compounds he should warn the patient to stop them if a skin eruption appears, and he must see the patient at intervals of at least once a month to check the blood count and watch critically for untoward reaction.

Anticonvulsants must be taken regularly each day. Divided doses are theoretically preferable but they are also forgotten more frequently. In my experience four doses daily has proved unsatisfactory. Middle-of-the-day medicine embarrasses children at school or adults at work. Consciously or unconsciously, they tend to omit it. Dividing the day's medication into two doses, morning and evening, and prescribing the hypnotic drugs after supper may prove most satisfactory.

If the patient must take medication more often, it is well for him to check on himself. An excellent method is for him to count out a week's supply into a separate container, and during the ensuing week take his tablets and capsules from this box. At the end of the week the forgotten doses in the container will loom as undeniable evidence of his neglect.

The patient must be comfortable with his medicine. The ideal anticonvulsant should have no action other than abolishing the epilepsy, but this goal has not been attained. We strive for this by limiting medication to the dose which the patient can take without suffering undesirable side effects. If a girl is distressed by hypertrophied gums and hirsutism, which may be the result of Dilantin, the doctor's therapeusis is scarcely praiseworthy even if the seizures have been controlled. The wage-earner cannot afford to be too sedated.

When medication has reached the ideal combination of control of seizures without undesirable reaction, it is best to keep the patient on it. It is the practice of some neurologists to maintain effective drug administration for a number of years after the last seizure. Just one ill-timed episode may cause loss of a driver's license, loss of a job or disruption of a home. Reports that a patient feels better than he has for years or that the child is doing well at school are indications to continue medicine, not to stop it. So long as the patient thrives, stick to the therapy; or, perhaps, increase it. The physician should be in close touch with his patient. During times of stress an increase in medication may be required. For example, a waiter had been sent out through union-hall hiring on many small jobs. Finally, his opportunity came when he was sent to one of the leading restaurants in the city for a permanent position. Although he had not had a seizure for over a year, a convulsion occurred the first day and

the job was lost. Had the physician known about the change of work, he would have advised an increase in dosage to cover the first few weeks at the new job.

A number of other factors should be discussed in addition to the use of anticonvulsant medication. The patient must abstain from the use of alcoholic beverages, including wine and beer. Occasionally, seizures appear to be precipitated by a very small quantity of liquor. Such seizures are proved to occur several days or a week after drinking. It is difficult or impossible to control epilepsy adequately if the patient persists in drinking. Young persons with epilepsy should be given to understand that being a teetotaler tends to enhance social acceptability rather than detract from it.

The excessive consumption of all liquids, including water, should be avoided. Hydration has been shown to precipitate convulsions. However, the patient must drink sufficient amounts to maintain health. He can be instructed to gauge the consumption of fluids by the output of urine. One or two liters of urine in 24 hours is usually satisfactory.

Excessive sodium in the diet causes retention of cellular fluids. Patients should refrain from taking too much salt; but the converse – a stringent low salt diet – does not seem to be indicated. A ketogenic diet, though impractical, has proved helpful in treating children but not adults.

Diet must be stressed, however, for patients whose blood sugar falls below normal. In this condition the patient should abstain from sweets and an excess of carbohydrates. Protein foods even though expensive should be increased in the diet. It is well to advise as much protein as is compatible with the family income, and the smallest amount of sweets as is agreeable to the patient. The therapeutic regime should be flexible, with compromises and exceptions when necessary. If the demands on the patient are too exacting, the added tension and frustration may outweigh the advantages of the restrictions.

So far as possible the person with epilepsy should not be made to feel different. An unhappy child at odds with his fellows is not our goal, but rather one who mingles freely and who regards his medication in the same category as codliver oil and his seizures like freckles.

Good health and normal muscular development favor control. Physical ailments should be combatted early. Patients should be advised to lead regular lives with adequate nutrition, excercise and sleep.

Finally, recreation is extremely important. Hobbies are good, but socialized activities are better. Epileptics tend to be self-conscious. They must be reassured and then urged into the social stream. In the treatment of children the physician must persuade the mother to let her child go with the others. It is not easy; the mother rightfully worries. But the child may have to take some chances in order to develop into a happy, useful citizen.

In the treatment of adults it is often necessary to encourage them to be self-supporting. Some epileptics gladly accept any job, and they should be given help in finding one. Others, self-conscious or too long out of work, shy away from employment and must be led back through sheltered workshops and other community projects. Then there are those, a minority, who remain wilfully dependent on government or industrial accident pensions. Some of these who have had a seizure at work claim and win industrial liability. This is grossly unfair to the majority who find it harder

as a result. If the physician points out from the first that a seizure occurring at work is not due to the work and that the patient is not entitled to compensation, the handicap to others in obtaining employment subsequently may be lessened.

In conclusion, epilepsy is controlled primarily by medication. The choice of anticonvulsants depends in part on the patient and in part on the nature of the seizures. Petit mal may respond to drugs which are unsatisfactory in treating the other types. In general, phenobarbital and Dilantin are safer and should be prescribed first. The newer drugs are to be used only when these have been found ineffective. At the beginning, drugs should be prescribed singly, and the dosage gradually built up to the patient's tolerance. Often a combination of drugs will prove far better than any one alone. Patients taking new anticonvulsants must be checked carefully at monthly intervals for signs of toxicity. Many patients should continue taking medication daily for life. Other factors in treatment include: complete abstinence from alcoholic beverages; restriction of fluid intake; general physical good health; recreation; and a productive and happy life.

The probability of a spontaneous arrest of the disease being so small, the next question becomes of paramount importance: What is the prospect of cure of the disease, or of arrest of the fits by treatment? The facts relating to the "cure" of the disease are extremely meagre, since very few cases can be watched sufficiently long to enable a cure to be confidently affirmed. As far as is known, however, the only method of cure is by obtaining arrest of the fits for a considerable time, and hence the answer to the second part of the question becomes practically the answer to the whole, as far as it can be given.

What is the prospect, in any given case, that an arrest of the fits can be obtained by treatment? The indications of the prognosis have been materially changed by the introduction of the bromides as remedies for epilepsy. Not only do they arrest fits far more frequently than any other remedy, but they are effective in many cases which, according to experience previous to the introduction of these remedies, would have been regarded as most unpromising. Hence, by their use, the conditions of the prognosis have been essentially changed. In order to ascertain how far the various conditions of the disease can be taken as indications of the amenability of a case to treatment, I have compared the facts of 43 cases in which no good was done by any method of treatment, with those of 100 cases in which the attacks were arrested by treatment as long as the patients remained under observation, all cases known to have relapsed being excluded. The number of cases is not large, but the conclusions agree with those which have been impressed on me by the observation of individual cases.

—W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Ben W. Lichtenstein, M.D.

CASE PRESENTATION

A 10 year old white girl was referred to the Illinois Neuropsychiatric Institute on May 26, 1952. Six months before entrance, her parents began to notice that the child appeared somewhat lazy. She no longer wished to play after coming home from school but preferred to lie down and sleep. At this time she developed anorexia and became somewhat finicky in her eating habits. This continued for about three months, after which her school teachers reported that she did her work poorly. Shortly afterwards the child was taken to the family physician who said that the child was only nervous and run-down, and he treated her symptomatically. One month before admission, she began to complain of occasional generalized headaches associated with nausea and vomiting. Although she had been a heavy drinker of milk since infancy, the parents noticed that they could not give her enough milk to satisfy her and that she began to resort to taking glasses of water about every 30 minutes. Examination at a local medical clinic revealed complete blindness of the right eye. Just before admission the child complained of rapidly alternating feelings of being hot or cold. Three days prior to admission she had frequent intense generalized headaches of a bursting nature associated with nausea and vomiting. There was a weight loss of ten pounds since the onset. The past history and the family history were not significant.

Physical examination: Examination revealed an apprehensive, asthenic girl who appeared to be chronically ill but not in any acute distress. She was oriented in all spheres and gave a reliable account of her illness. The right eye was completely blind, its disc showing primary optic atrophy and an old patch of chorioretinitis. The acuity in the left eye was 20/70, and confrontation tests indicated a temporal hemianopsia. The left optic disc appeared normal. The right pupil was larger than the left and did not react to light, though it did react consensually. There was no facial, lingual or palatal palsy. In the spinal distribution, the motor, sensory, reflex and coordination system were intact.

Urine and blood examinations were not significant. An electroencephalogram made on June 3, 1952, revealed a basic frequency of 3 to 5 per second, with a slow wave focus in the right frontotemporal areas while awake and asleep. X-ray of the chest was normal. Views of the optic foramina revealed no enlargement. Roentgenograms of the skull revealed enlargement of the sella turcica with thinning of the dorsum. This was interpreted by the radiologist as being consistent with a primary pituitary tumor or optic glioma with involvement of the chiasm. Because of the headache and vomiting a lumbar puncture was not performed.

CLINICAL DISCUSSION

DR. LICHTENSTEIN: Dr. Oldberg, would you please comment on the diagnostic problem presented by this case?

DR. ERIC OLDBERG: Here is a 10 year old girl just embarking upon the second decade of life. If she has a space-occu-

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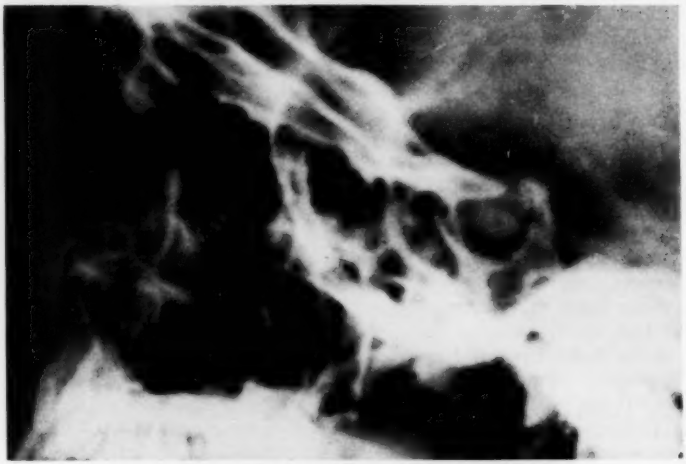

FIG. 1. Roentgenogram of the sella turcica and its neighborhood.

pying lesion, the type most common at this age is a craniopharyngioma. During the three months before admission to the hospital she became increasingly somnolent; shortly before admission, there was an increase of fluid intake. The lesion which most usually produces these symptoms is a craniopharyngioma. In addition, she had blindness of the right eye and a diminution of vision of the left eye, indicating that something produced chiasmal pressure. That one eye was more affected than the other is also characteristic of craniopharyngioma, which is not fixed in the midline like a pituitary tumor and which frequently involves one nerve earlier than the other. The sella turcica is enlarged—more on one side than on the other.

As symptoms indicate, toward the end of the course she became decompensated as far as ability to harbor this tumor; she developed increased pressure, vomiting and headache. There were no choked discs. The size of the lesion is not diagnostically indicated by the fact that she had slow waves in the electroencephalogram on the side of her blind eye. A cyst connected with the tumor might possibly, not probably, extend out into the hemisphere on that side. X-ray of the skull shows a sella which, for a child with no eye findings, would probably be considered within normal limits for size. An area inside the sella looks as though there might be calcification inside, but I would like to look at a stereoscopic set to be sure. I do not see any suprasellar calcification in these films. I do see, however, in the lateral plates, convolutional markings which might be little more than normal for a 10 year old. There may be a little more than normal separation of the sutures, compatible with the headaches and vomiting with pressure resulting from blockage of the exit of fluid from the third ventricle. In another view, the posterior clinoid on the right appears somewhat ragged as compared to the relatively smooth posterior clinoid on the left; this fits in with the fact that her vision in the right eye was more dis-

turbed, and with the fact that that eye was the first to be affected.

DR. LICHTENSTEIN: Dr. Sugar, would you care to add to Dr. Oldberg's discussion?

DR. OSCAR SUGAR: Yes, I would. Not only is the right posterior clinoid eroded but the right petrous bone also looks as if it has a hole in it. This might indicate something which ran all the way back from the eye to the petrous bone. I, therefore, am inclined to consider such a rare lesion as a malignant tumor of the roof of the nasopharynx or the base of the skull. Pituitary tumor need not be seriously considered; it rarely occurs in this age group.

DR. LICHTENSTEIN: Dr. Garvin, have you any comment to make?

DR. JOHN S. GARVIN: The most likely cause of this syndrome is a craniopharyngioma. However, the possibility of a glioma of the optic chiasm which might be extending back to involve the hypothalamus must also be considered.

DR. LICHTENSTEIN: Dr. Oldberg, would you please discuss your operative findings?

DR. OLDBERG: I performed a right frontal exploration of the type usually used for pituitary tumor. When the optic chiasm and pituitary region were exposed, I encountered a friable tumor which did not appear to be originating directly from the pituitary but rather from the suprasellar region. A considerable amount of tumor tissue was removed and, when hemostasis was complete, closure was performed in the usual manner.

DR. LICHTENSTEIN: Dr. Bailey, would you please comment on the surgical biopsy?

DR. PERCIVAL BAILEY: The tissue removed at operation consisted of numerous small fragments of friable tissue with insufficient connective tissue to hold them together. It consisted of small cells with very little cytoplasm and without architectural arrangement. The nuclei were small and oval, and many mitoses were seen. This tissue was interpreted as being a malignant tumor of the anterior lobe of the hypophysis, which is often called carcinoma in the literature.

DR. LICHTENSTEIN: The child returned from surgery in good condition. The next day she was responsive and active, and recognized the doctors and her parents. On the second postoperative day it was noted that her course was surprisingly smooth and she was taking fluids by mouth. By June 12 the postoperative edema of the eyelids had disappeared but no improvement in vision was noted. On June 20 the patient complained of mild headache, nausea and vomiting. The headaches continued, and on June 23 she became very drowsy and lapsed into a state of shock. When respirations failed, she was placed in a mechanical respirator and was given intravenous infusions of norepinephrine and 2 units of ACTH. She continued in a state of coma with hypothermia and imperceptible pulse. Her condition was believed to be due to hypopituitarism, and replacement therapy was attempted. Despite these measures she died on June 25.

Dr. Bailey, would you please comment on your examination of the brain in this case?

PATHOLOGIC DISCUSSION

DR. BAILEY: When the brain was sectioned, it was seen that the third ventricle was filled with this mass of friable tumor, which extended from the pineal region to the hypophysial region. No pineal body was found, either macroscopically or microscopically, and the tissue did not involve the hypophysial gland but remained above the diaphragma sellae. The tumor is extensively degenerated but, in areas in which the tissue is healthy, it can be seen that there is a mixture of two types of cells—

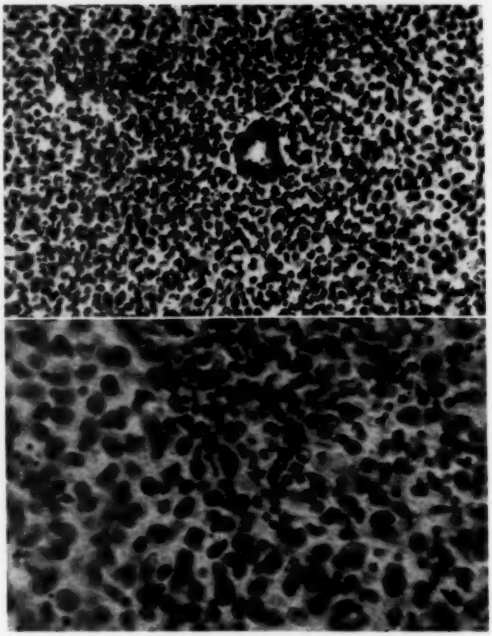

FIG. 2. Low power photomicrograph showing one of the many ependymal tubules found in the tumor. Thionin stain.

FIG. 3. Higher power photomicrograph showing the large cells and small lymphoid cells which are characteristic of a pinealoma. Thionin stain.

small cells looking somewhat like lymphocytes, and others with larger nuclei, such as were seen in the surgical material. This combination is characteristic of the tumors which develop from the pineal primordium, and such tumors are called pinealomas. In addition, one sees, in this tumor, small canals lined by cylindrical epithelium which resemble the ependymal tubules seen in the central canal of the spinal cord or near the aqueduct of Sylvius when there is abnormal development of this latter structure. These are undoubtedly ependymal tubules, and their presence in pinealomas, though rare, is easily explicable, since the pineal body develops from the ependymal roof of the third ventricle.

DR. LICHTENSTEIN: Dr. Sugar, do you have any comments on the postoperative course of this patient?

DR. SUGAR: Yes, I have. There seems to be a growing tendency in pediatric neurosurgery to start patients on cortisone before an exploration of the chiasm; the cortisone is continued during the operation and some days thereafter to tide the patient through possible pituitary insufficiency. If ACTH is used, it should be started some days before the operation, whereas cortisone may be started just a day before.

DR. LICHTENSTEIN: This case illustrates very well that neurologic signs and symptoms are more indicative of the site than the nature of the pathologic process. By correlating the site of dysfunction in the nervous system, the course of the disorder, and the associated physical findings, if any, with the natural history of disease entities, we are able to approximate a correct diagnosis in most instances. The diabetes insipidus, visual disturbances, and somnolence

were indicative of a hypothalamic lesion. The headache, vomiting and early signs of increased intracranial pressure pointed to a space-occupying lesion rather than to an inflammatory or degenerative disorder. On the basis of the history, findings and course, a craniopharyngioma was the most likely diagnosis, and it was good to see that Drs. Oldberg and Garvin considered this diagnosis in the absence of physical signs suggestive of other pathologic processes. Dr. Sugar seems to have felt that I would not pick a straightforward case for presentation, and he tended to consider invasion of the base of the skull by a malignancy from the nasopharynx. There was no evidence of enlargement of the optic foramina or cutaneous signs of von Recklinghausen's disease of the nervous system to suggest glioma of the optic chiasm and extension into the optic nerves. Hand-Schüller-Christian disease was a possibility because of the questionable erosion of the skull at the base, but the absence of lesions in other bones and the absence of exophthalmos or signs of adiposogenital dystrophy made such an impression unlikely. Neurocytomas of the adrenal medullae spread extensively, and, in the Hutchison[1] type, metastases to the skull are common, but the orbit is generally affected first and the course is much more malignant than in the case presented. The midline of the developing embryo is frequently the site of malformations, and one would have to consider teratomas and dermoids arising in the parapituitary region.

The difficulties in making an exact diagnosis from a surgical biopsy is again illustrated. The tumor was extensively necrotic, and it is only natural for the pathologist to consider likely possibilities when he is forced to commit himself. Since glioma of the floor of the third ventricle, whether pineal, ependymal, or subependymal in origin, gives identical clinical pictures, I know of no means of making a final diagnosis without employing histopathologic identification.

DR. OLDBERG: I would like to supplement Dr. Lichtenstein's summary by saying that I believe it is still the practical thing to make a working diagnosis of the most common type of lesion which produces a given symptom-complex and neurologic findings, particularly if that lesion far exceeds in number all other pathologic possibilities which might produce the same syndrome. Indeed, in this instance, since the site of origin of the lesion found at autopsy seemed to be in the neighborhood of the pineal body, we must recognize that, preoperatively, no interference with ocular movement had been observed; on the other hand, it was definitely noted that pupillary reactions existed, though they were only consensual in the blind eye. In other words, this tumor, instead of extending toward the quadrigeminal bodies, blocking the aqueduct early, and involving cerebellar connections early, took the course described by Horrax[2]—extending downwards into the region of the posterior lobe of the pituitary body, which I imagine was the reason for the difficulty with water balance. This could cause disturbance of the supraopticohypophyseal tract. In short, this tumor did not produce the symptom-complex usually found in tumors originating in the pineal, but instead extended away from that site to produce the hypothalamic picture already described.

DR. LICHTENSTEIN: I wish to thank all of you for your cooperation in making this clinical pathologic conference a success.

Pathologic diagnosis: Pinealoma.

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CASE REPORT

Increased Intracranial Pressure following Compression of the Superior Sagittal Sinus

C. M. Caudill, M.D., L. A. French, M.D. and G. L. Haines, M.D.

THIS report presents a case in which evidence of increased intracranial pressure developed slowly following compression of the superior longitudinal sinus in the posterior parietal area by a depressed bone fragment. Dural sinus pressure recordings and venograms before and after elevation of the fragment were performed by Ray's method.[1] The evidence of increased intracranial pressure resolved following removal of the compression.

Wharton[2] in 1901 published a detailed report on traumatic involvement of the dural sinuses in which he collected 65 cases from the literature and reported on five of his own. He recognized certain dangers associated with elevation of the bone fragments, such as profuse hemorrhage, thrombosis and air embolism. He did not stress the syndrome resulting from compression of the sinus.

It was not until 1915 when Holmes and Sargent[3] reported 78 cases of traumatic obstruction of the superior longitudinal sinus that the syndrome resulting from occlusion of the superior longitudinal sinus at or posterior to the Rolandic veins was emphasized. In their reported cases the syndrome varied in severity from involvement of one leg to a spastic quadriplegia. At least one arm was affected in 57 of the 78 cases, but never were the face or speech affected. When the lesion was located more posteriorly, a marked disturbance was observed in stereognosis, position sense, and two-point discrimination. Also retention of urine was common, focal seizures occurred in 15 per cent of patients, and papilledema was observed frequently. Subsequently others have reported on the symptomatology and complications of dural sinus injury.[4–10]

CASE SUMMARY

A 57 year old white male was struck on the top of his head by a revolving airplane propeller. He was unconscious for a few moments, but he became lucid and cooperative immediately therafter. The scalp laceration was sutured. The patient was referred to the hospital two days later (December 22, 1950) because of progressive development of headache, dizziness, tinnitus and drowsiness.

From the division of neurosurgery, department of surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

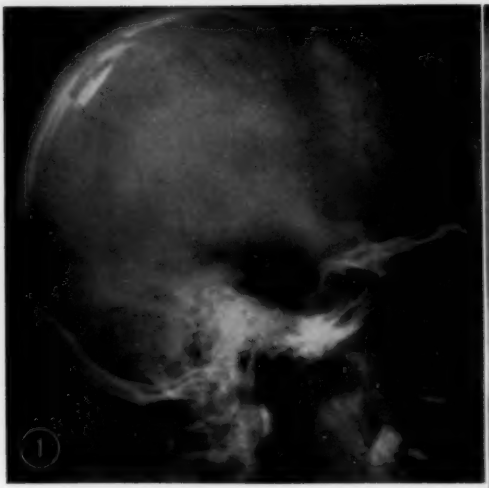

FIG. 1. Roentgenogram showing depressed fracture over the sagittal suture in the parietal area.

FIG. 2. Roentgenogram after injection of sagittal sinus with 35 per cent Diodrast. The dye can be seen in the veins draining anteriorly; none of the dye passes posteriorly through the sinus.

Examination at the time of admission showed the patient to be cooperative despite mild confusion, headache and drowsiness. Blood pressure was 150/90, and a grade III apical systolic murmur was heard. The scalp wound consisted of two parallel lacerations 10 cm. in length located in the parietal area and coursing obliquely backwards across the midline from right to left. There was considerable necrotic drainage from the wound. The patient was given massive doses of penicillin and Streptomycin. Skull roentgenograms revealed a depressed fracture located over the sagittal sinus in the posterior parietal region (figure 1).

The day after admission the patient remained drowsy and the complaints of headache increased. Spinal puncture showed a pressure of 560 mm. of water. Papilledema appeared three days later and gradually increased in severity until the time of operation. The visual acuity remained unchanged.

On January 3, 1951, 14 days after the injury, Diodrast injection of the superior longitudinal sinus revealed an apparently complete obstruction at the site of the depressed fracture (figure 2). With the patient in the horizontal position, the pressure within the sinus exceeded by 330 mm. of water the venous pressure measured in the antecubital space.

The following day the depressed bone fragments along with much necrotic granulation tissue were removed. Greatly increased bleeding from all the exposed tissue including the cranium was observed until the compression of the sagittal sinus was relieved. This increased vascularity then subsided. The pressure in the sagittal sinus was measured immediately after removal of the compression, and it was found to equal the pressure in a vein in the antecubital space. Diodrast injection of the sinus revealed no block.

Immediately postoperatively the patient was relieved of the headaches. Spinal fluid pressures on the first and fifth postoperative days were 170 and 150 mm. of water respectively. When ambulation was undertaken the patient had a staggering gait and he complained of tinnitus and dizziness. All these symptoms diminished gradually and three weeks postoperatively he was asymptomatic. Examination of visual fields and fundi revealed no abnormality.

The patient was seen one year following the injury and he was still asymptomatic. There were no neurologic abnormalities.

PRESSURE MEASUREMENTS

	Venous (antecubital space)	*Sagittal sinus*	*Lumbar subarachnoid space*
Preoperative . . .	90	420	560
Postoperative . . .	100	100	170

COMMENT

This case reiterates the observation of Holmes and Sargent[3] that dural sinuses can be occluded by overlying depressed fractures. However, from the operative and autopsy findings of these authors the basic occlusion appeared to be thrombosis of the sinus and of its contributory venous lakes and veins. In the case presented above delay of definitive surgery was necessitated by the obvious contamination of the wound. This circumstance allowed the observation that a dural sinus can be occluded by external pressure alone, with the secondary production of increased intracranial pressure. The absence of thrombosis undoubtedly accounted for the lack of very severe neurologic changes in this patient compared to those patients of Holmes and Sargent. In the present case blood was shunted forward because of the posterior obstruction, whereas, in their cases the venous thrombosis precluded any shunting of the flow of blood. Likewise, the slow recovery in their patients was justly attributed to the slow establishment of collateral circulation.

The lack of any evidence for thrombosis in this patient is in accordance with the observation of Beck and Russell[6] that experimental thrombosis of dural sinus is very difficult to produce.

The facts in this case clearly indicate that simple, acute occlusion of the superior longitudinal sinus can produce a high degree of increased intracranial pressure. This is of vital importance to the surgeon who is removing a lesion such as a parasagittal meningioma because it shows the potential danger of the ligation of a patent sinus, especially if this is done as far posteriorly as the midparietal region. Jaeger[11] has reported the successful resection of a partially patent sinus in a patient with a parasagittal meningioma in the posterior third of the sinus. This patient undoubtedly had developed adequate collateral circulation prior to the sinus resection.

It is believed that the presented case gives supporting evidence to the concept that, at least in certain instances, the symptoms of increased intracranial pressure observed in patients with "otitic hydrocephalus" and "pseudotumor cerebri" can be due to sinus thrombosis.[12] The usefulness of sinus pressures and dural sinus venography in differentiating such lesions is apparent.

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11. Jaeger, R.: Observations on resection of the superior longitudinal sinus at and posterior to the Rolandic venous inflow, J. Neurosurg. 8:103, 1951.
12. Ray, B. S., and Dunbar, H. S.: Thrombosis of the dural venous sinuses as a cause of pseudotumor cerebri, Ann. Surg. 134:376, 1951.

PROGRAM OF THE

AMERICAN ACADEMY OF NEUROLOGY

Fifth Annual Meeting

April 9, 10 and 11, 1953

Edgewater Beach Hotel — *Chicago, Illinois*

Review Courses in Basic and Clinical Neurology

April 6, 7, 8, 1953

Intensive review courses in basic and clinical neurology will be given preceding the annual meeting, sponsored and arranged by the American Academy of Neurology.

Courses will be held as follows:

Neuropathology—April 6, 1953

Neuroroentgenology—April 6 and 7, 1953

Clinical Electroencephalography—April 6, 1953

Special Problems in Clinical Electroencephalography—April 7, 1953

Episodic Disturbances of the Nervous System—April 7, 1953

Clinical Neuro-ophthalmology – April 7, 1953

Language Disabilities—April 8, 1953

Brain Tumors—April 8, 1953

Neurologic Anatomy —April 8, 1953

Additional information regarding these review courses may be obtained by writing to Dr. A. B. Baker, 19 Millard Hall, University of Minnesota, Minneapolis 14, Minnesota.

THURSDAY, APRIL 9, 1953

Morning Session 9:00 a.m.

Chairman: Morris B. Bender, M.D., *New York City*

Secretary: Morton Nathanson, M.D., *New York City*

What EEG Can Never Show

Warren S. McCullough, M.D., *Cambridge, Massachusetts*

The Effect of Mesencephalic and Posterior Hypothalamic Lesions on the Cortical Electroconvulsant Threshold

David A. Freedman, M.D., and John Moossy, M.D., *New Orleans, Louisiana*

Clinical and Electroencephalographic Studies of Patients Developing Encephalitis Following Measles

Herbert Grossman, M.D., E. L. Gibbs, M.D. and Catherine L. Rich, M.D., *Chicago, Illinois*

Toxoplasmosis of the Nervous System

Abner Wolf, M.D., *New York City*

Iceland Disease: A new infection simulating acute anterior poliomyelitis

D. Naldrett White, M.D., *Kingston, Ontario* and Robert B. Burtch, M.D., *Alexandria Bay, New York*

Studies on the Extraneural Phase of Experimental Poliomyelitis

G. Schwartzman, M.D. and S. A. Aronson, *New York City*

Business Session 11:30 a.m.

Pearce Bailey, M.D., retiring president, presiding

THURSDAY, APRIL 9, 1953

Afternoon Session 2:00 p.m.

Chairman: Alexander T. Ross, M.D., *Indianapolis, Indiana*

Secretary: Philip T. White, M.D., *Rochester, Minnesota*

Angiographic Evidence of Arterial Spasm in Cerebral Vascular Disorders

Arthur Ecker, M.D. and Paul Remenschneider, M.D., *Syracuse, New York*

Blood in the Subarachnoid Space: A clinical evaluation of the occurrence in 190 consecutive cases

Morton Nathanson, M.D., Alvin Robins, M.D. and Martin Green, M.D., *New York City*

Experiences with Imperception and Anosognosia

I. S. Freiman, M.D., A. Robins, M.D. and E. D. Friedman, M.D., *New York City*

Memory as a Biologic Function

Roland P. Mackay, M.D., *Chicago, Illinois*

The Differences Between Voluntary Ergograms and the New Electronic Ergogram in Neurological Conditions

Robert S. Schwab, M.D., Thomas L. Delorme, M.D. and Margaret Gray, M.D., *Boston, Massachusetts*

The Effect of Intravenous Barbiturates on Abnormal Involuntary Movements

Philip S. Bergman, M.D., Morton Nathanson, M.D. and Morris B. Bender, M.D., *New York City*

The Use of Piromen® in Central Nervous System Injury—A Preliminary Survey

Pearce Bailey, M.D. and Walter J. Friedlander, M.D., *Bethesda, Maryland*

Diffuse Leptomeningeal Carcinomatosis: Clinical and Pathological Characteristics

G. O. Grain, M.D. and J. P. Karr, M.D., *Detroit, Michigan*

FRIDAY, APRIL 10, 1953

Morning Session 9:00 a.m.

Chairman: Russell N. DeJong, M.D., *Ann Arbor, Michigan*

Secretary: Kenneth R. Magee, M.D., *Ann Arbor, Michigan*

Lobotomy and Epilepsy: Incidence of seizures in 1,000 cases

Walter Freeman, M.D., *Washington, D.C.*

Convulsions in the Aged

Philip T. White, M.D., Allan A. Bailey, M.D. and Reginald G. Bickford, M.D., *Rochester, Minnesota*

Brain Tumors in Patients Over 60 Years of Age

Charles Rupp, M.D., Helena E. Riggs, M.D., *Philadelphia, Pennsylvania,* H. W. Hogan, M.D., *Canton, Ohio* and James L. Moulton, M.D., *Cincinnati, Ohio*

Prenderol, A New Drug Effective in Petit Mal Epilepsy

M. A. Perlstein, M.D., *Chicago, Illinois*

The Use of Mysoline in Epilepsy

Vasilios S. Lambros, M.D., *Washington, D.C.*

Copper Balance Studies in Hepatolenticular Degeneration: The effect of administration of 2, 3-dimercaptoprotanol (BAL)

Walter T. Zimdahl, M.D., Irving Hyman, M.D. and Edward Cook, M.D., *Buffalo, New York*

11:00 a.m. Presidential Address
Pearce Bailey, M.D.

11:30 a.m. Business session

FRIDAY, APRIL 10, 1953

Afternoon Session 2:00 p.m.

Chairman: Roland P. Mackay, M.D., *Chicago, Illinois*

Secretary: H. William Gillen, M.D., *New Orleans, Louisiana*

Studies in Neuromuscular Diseases with Radioactive Potassium

W. H. Blahd, M.D., F. K. Bauer, M.D., R. L. Libby, M.D. and A. S. Rose, M.D., *Los Angeles, California*

Observations on Pentosuria in Neuromuscular Disorders

A. L. Drew, M.D. and B. T. Selving, M.D., *Ann Arbor, Michigan*

Structure and Biologic Activity of Compounds in Muscular Dystrophy in Rabbits

M. C. Farber, M.D., A. E. Milman, M.D. and A. T. Milhorat, M.D., *New York City*

Observations on Fiber Specificity in Cutaneous Innervation

Roger Sperry, M.D., *Chicago, Illinois* (by invitation)

Porphyria—A Clinical and Neuropathologic Report

Gabriel A. Schwarz, M.D., *Philadelphia, Pennsylvania* and James A. L. Moulton, M.D., *Cincinnati, Ohio*

The Therapy of Myasthenia Gravis

Paul F. A. Hoefer, M.D., Henry Aranow, Jr., M.D. and Lewis P. Rowland, M.D., *New York City*

Circulatory Changes in the Hamster's Cheek Pouch Associated with Alimentary Lipemia

Roy L. Swank, M.D. and Chester F. Cullen, M.D., *Montreal, Quebec*

Quantitative Method for the Determination of Gamma Globulin in the Cerebrospinal Fluid and Its Application to Multiple Sclerosis

Elizabeth Roboz, M.D., Walter C. Hess, M.D. and Francis M. Forster, M.D., *Washington, D.C.*

SATURDAY, APRIL 11, 1953

Morning Session 9:00 a.m.

Chairman: Russell Costello, M.D., *Detroit*, Michigan

Secretary: William C. Noshay, M.D., *Detroit, Michigan*

The Relationship of Homologous Brain Proteolipide to Allergic Encephalomyelitis in Guinea Pigs

N. P. Goldstein, M.D., A. Karlson, M.D., L. C. Kolb, M.D., H. Mason, M.D. and G. Sayre, M.D., *Rochester, Minnesota*

Variability of the Course of Guillain-Barre Syndrome: Recrudescence during period of apparent recovery

Benjamin Boshes, M.D. and Irving C. Sherman, M.D., *Chicago, Illinois*

Recent Advances in the Study of Cerebral Circulation

Seymour S. Kety, M.D., *Bethesda, Maryland*

Brain Stem Syndromes: Metencephalitis versus Intrapontine Gliomata

John B. Pfeiffer, Jr., M.D. and Frank L. Wrenn, M.D., *Durham, North Carolina*

Familial Primary Amyloidosis with Nervous System Involvement

Artin D. Kantarjian, M.D. and Russell N. DeJong, M.D., *Ann Arbor, Michigan*

Management of Chromophobe Pituitary Adenoma

Carl F. List, M.D., *Grand Rapids, Michigan*

Actinomycosis of the Nervous System

Harold Stevens, M.D., *Washington, D.C.*

12:00 Adjournment

PAPERS READ BY TITLE

The Lateral Medullary Syndrome

Lewis Levy, M.D., Irving O. Dein, M.D. and Ephraim Roseman, M.D., *Louisville, Kentucky*

Cholesteatoma of the Basilar Bone Simulating Pinealoma

Guy H. Williams, Jr., M.D. and W. J. Gardner, M.D., *Cleveland, Ohio*

Paroxysmal Disorder on the Basis of Pancreatic Adenoma

Israel H. Schuleman, M.D. and Hamilton Ford, M.D., *Galveston, Texas*

The Functional Organization of the Central Nervous System with Respect to Orientation in Time

John Campbell, M.D., *Cincinnati, Ohio*

Is Order of Birth a Factor in Epilepsy?

Joseph K. Orr, M.D. and Frank Risch, M.D., *Los Angeles, California*

Neurology BOOK REVIEWS

The Autonomic Nervous System

James C. White, M.D., Reginald H. Smithwick, M.D. and Fiorindo A. Simeone, M.D. 1952. New York: The Macmillan Company. 569 pages. $12.00.

This, the third edition, has been carefully and extensively revised. It represents a comprehensive survey of the anatomy, physiology, and surgery of the autonomic nervous system.

A critical reading of the chapters dealing with the structure and function of the autonomic nervous system reveals concern for accurate editing and exposition. It is apparent that the authors took the time and effort to consult authoritative opinion in the basic scientific fields. They do not hesitate to take a stand on controversial issues; the range of clinical observations and the results of numerous operations give a note of sureness which will be welcomed by most readers. The reviewer was impressed by the forthright handling of the problem of nomenclature, the problem of visceral pain, and the frequently debated issue of active vasodilator and secretory fibers.

In the clinical discussions the authors are, of course, especially at home. This section deals systematically with various diseases wherein operative procedures on the autonomic nervous system may be applied. The presentation is quite inclusive: peripheral vascular diseases, bone disease, angina pectoris and hypertensive cardiovascular disease, painful states in other viscera. A chapter is devoted to the surgery of the autonomic nervous system in disorders of the brain and meninges; in the matter of stellate block as a mode of treatment for cerebral thrombosis and embolism, the authors conclude with this view, "Our experience to date has left us unconvinced of the value of the procedure."

The case reports used to illustrate the general discussion will be appreciated—and the selection of patients with an unusually high recovery rate will be readily pardoned.

A. B. V.

A Textbook of Clinical Neurology

Israel S. Wechsler, M.D. 1952. Philadelphia: W. B. Saunders Company. 801 pages, $9.50.

The seventh edition of this well-known work recalls the fact that it was first published 25 years ago. Much of the original remains, though advances in knowledge of diseases of the nervous system have necessitated deletions and additions to the text. It is much to the credit of the author that this has been done without adding to the bulk of the book, so that all descriptions remain fairly comprehensive, yet well within the grasp of the medical student. The fa-

miliar chapter on psychological diagnosis by David Wechsler is again presented.

The book follows the standard pattern expected of a medical textbook. The basic data of the neurologic examination and nervous diseases are presented concisely and, in general, quite adequately. Teachers of the subject, of course, will agree or disagree with some points, but taken as a whole the book will continue to be regarded as a good working presentation of the subject for student and for general use.

A. R. V.

Foundations of Neuropsychiatry

Stanley Cobb, M.D. Fifth edition. 1952. Baltimore: Williams and Wilkins Company. 287 pages, $3.00.

This book has stood the test of four editions in a decade and so hardly needs a recommendation to the medical public. Its popularity among medical students and physicians is understandable. It is one of the very few and very much needed texts which attempt to present the anatomy, physiology, neuropathology, psychology, psychopathology and philosophy of medical sciences in a sequence of integrated arguments. The manner of treatment of the entire range of subjects is highly personal to the author and a product of long experience and thought in handling his subject didactically before an audience of medical students and of neurologic and psychiatric residents. The book is written with meticulous care for simplicity and clarity of language.

The unity of the goals of all sciences dealing with the organization of human behavior is the keynote of the book. The position of the author is essentially organismic, i.e., holistic, although pluralistically applied at different levels of his well known "pyramid" of psychiatry, from basic sciences ex-acto mensurandi, such as physics and chemistry, to the apical sciences ex-perimento vivendi, such as psychoanalysis and theoretical psychology.

The first five chapters of the book represent a compendium of anatomy and physiology of the nervous system. The range of factual information, which the author condensed into the 100 pages of these five chapters and yet managed to order the facts so that they are meaningful, represents a remarkable accomplishment. These first five chapters are concluded with a chapter on "Consciousness and 'Mind-Body' Problem." Chapters seven through eleven deal with physiology of the cerebral circulation, cerebrospinal fluid, and general and special neuropathology. Chapter twelve summarizes the anatomic, physiologic, and psychopathologic problems of epilepsy. In chapter thirteen the author deals with some psychological concepts important in medicine, such as the concepts of instinct, intelligence, memory, attention, learning and emotions. Chapter fourteen concludes the book with the author's theory of multiple causation, classification of psychiatric disorders, and a concise discussion of psychoneuroses, psychosomatic disorders, and schizoaffective reactions.

Each chapter is supplied with a bibliographic list of critical references. The book should be eminently useful not only to medical students, but also to physicians, especially neurologists and psychiatrists. Some of the latter who are beset with the anguishing prospect of board examinations should find in this book not only a readable and comprehensive compendium of the so-called "basic" neurology and psychiatry but also a help in understanding the reciprocal relevancy of anatomy, neurology, psychology and psychiatry. P. I. Y.

Neurology

Pathologic Changes in the Brain in Coma Following Ether Anesthesia

John Denst, M.D.

On rare occasions coma and death follow ether anesthesia. The cerebral lesions which were observed in three cases of postanesthetic coma are presented in this study. In none of these patients was death directly attributable to faulty administration of the ether, to obstruction of the airways, to shock, or to respiratory or cardiac arrest. No pre-existing potentially fatal disease conditions were found at autopsy. Little information is available in the literature regarding the nature of the cerebral alterations induced by ether, although clinical and pathologic reports of the lesions caused by nitrous oxide, anoxia, and cardiac arrest are more numerous. One of the problems requiring attention is whether ether has a selective action of certain areas of the brain, or whether it produces non-specific anoxic lesions.

REVIEW OF LITERATURE

Weber[1] reported the case of a four year old diplegic idiot who apparently suffered irreversible cerebral cortical injury, when, at the age of two years, he was given an ether anesthetic for an appendectomy. Courville[2] described three patients with neurologic symptoms which attended the use of ether. One patient, a 30 year old woman, developed lasting spasticity and a psychosis after surgery for a Bartholin gland abscess. Another patient, eight months of age, became cyanotic during circumcision and had postoperative coma. He improved, but at the age of 26 years he exhibited general athetosis.

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The third patient was a 29 year old woman who developed decerebrate rigidity and blindness following cardiac arrest under ethyl chloride-ether anesthesia. Zweighaft[3] published a case of hemiplegia which followed tonsillectomy under open drop ether anesthesia, without the observance of any anoxic episode during the procedure; complete recovery occurred. Pisetsky[4] also reported a case of hemiplegia as a complication of ether anesthesia. Burdick, Lisa and Elias[5] described cerebral infarction following administration of ether to a patient with massive wound hemorrhage and severe cerebral arteriosclerosis. Tye[6] reported cortical necrosis in a ten year old boy who had had convulsions during an appendectomy under ether-nitrous oxide anesthesia, with subsequent coma and decerebrate rigidity for 29 days. Pathologic observations in cases of ether anesthesia complicated by cardiac arrest were reported by Kemp,[7] Waddy[8] and Lenahan.[9]

REPORT OF CASES

Case 1.—An eight year old white boy, in apparently good general health, had a tonsillectomy under ether, administered by the open drop method following ethyl chloride induction. The pre-operative medication was morphine sulfate (gr. ¼). The operation was well tolerated, but during the first eight postoperative hours the patient could not be aroused from what appeared to be a deep sleep; his color and breathing were normal. He then awakened momentarily and vomited. During the next seven hours he developed delirium, Cheyne-Stokes respiration, carpopedal spasm, loss of the tendon reflexes, and dilated pupils. By the end of this time the body and extremities were extended rigidly. The temperature rose to 106° F. The spinal fluid was clear and under normal pressure. The spasticity decreased during the next four days, except for the persistence of slight nuchal rigidity. Oliguria and albuminuria commenced at the time of the operation, and thereafter the flow of urine was almost entirely suppressed. The blood nonprotein nitrogen rose to 144 mg. per cent. To alleviate the uremia, the peritoneal cavity was irrigated daily from the sixth to the nineteenth postoperative days, with 30 to 40 liters of Tyrode's solution containing 1.75 per cent glucose. Urinary output by the end of this time rose to a maximum of 2700 cc. a day. The uremia also improved. The blood pH ranged from 7.5 to 7.8 before and after peritoneal irrigation. The patient never emerged from the coma. He responded to painful stimuli with aimless movements. He had an irregular hyperpnea. The blood pressure was elevated to as much as 200/122. On the fifteenth day the spinal fluid was colorless. On the thirtieth day the spinal fluid contained 230,000 erythrocytes and 1,800 leukocytes per cu. mm. On the thirty-third day, erythrocytes numbered 9,760 per cu. mm., and leukocytes 820 per cu. mm. Shortly before his death on the thirty-fifth postoperative day, a physical examination disclosed slight nuchal rigidty, positive hard palate and sucking reflexes, and hyperactive patellar and adductor reflexes.

AUTOPSY

The body was well developed and well nourished. Crusted surgical scars, each 2 cm. long, were present on the abdomen 2 cm. superior to each inguinal ligament. Delicate fibrous adhesions coated the small intestine. The heart weighed 205 gm. and showed left ventricular hypertrophy. Small patches of bronchopneumonia were present in the lungs. The kidneys together weighed 360 gm., and they were smooth, soft and dark red. The cortices measured 11 mm. thick and contained many minute abscesses. Microscopically, partly healed miliary abscesses were present. The major portion of the renal parenchyma appeared normal.

Brain: After embalming, the brain weighed 1465 gm. A small aneurysm of the proximal portion of the right anterior cerebral artery was ruptured. Recent hemorrhage slightly

thickened the leptomeninges covering the base of the brain, the cerebellum, and to a lesser degree the convex surface of the cerebrum. No subdural hemorrhage was present. Extensive, almost symmetrical, bilateral softenings of the white matter in the superior halves of both cerebral hemispheres extended from the occipital lobes, through the parietal lobes, and into the frontal lobes. The color of the softened white matter was similar to that of the gray matter. Pale yellow foci and small hemorrhages were present in the softened areas. The cortex and subcortical white matter appeared intact. The right caudate nucleus and the medial portion of the right globus pallidus were stippled with petechiae. The slightly dilated lateral ventricles contained thin brown fluid. Cerebellum, pons, and medulla appeared structurally normal. The meninges covering the entire length of the spinal cord were greatly thickened by fresh hemorrhage.

Cerebrum: Microscopically, broad areas of the deep convolutional and central white matter exhibited advanced necrosis, with massive proliferations of gitter cells and capillaries, and with small isolated old and recent focal hemorrhages (figure 1). The adjacent subcortical white matter showed diffuse proliferations of microglial cells and astrocytes, and the myelin sheaths were little damaged. The internal capsule, where it merged with the basis pedunculi, was encroached upon by the hemorrhage from the aneurysm and was necrotic and heavily infiltrated with polymorphs. The laminar structure of the cortex was not disturbed. A few ghost cells were present in all layers. Scattered cells were shrunken and showed loss of Nissl substance. Some nuclei were lobulated, elongated, pale or pyknotic, and had eccentric nucleoli. A slight diffuse proliferation of protoplasmic astrocytes was present throughout the cortex. This glial reaction was most pronounced in the superficial and deepest zones of the insular and occipital cortex. Microglia, rod cells, and swollen oligodendroglia were also present in these areas. No fibrillary gliosis was observed. In every section of the frontal, parietal, and occipital lobes, the cortex contained at least one discrete, richly cellular granulomatous nodule (figure 2). Each of the granulomas was composed of giant cells, which possessed homogeneous or coarsely vacuolated cytoplasm and a peripheral ring or horseshoe-shaped cluster of nuclei. Large mononuclear cells with nuclei similar to those of astrocytes were numerous. Small dark nuclei and rod cells were also present. One of the cortical nodules was situated in close relation to an arteriole, which branched from a pial vessel, and whose wall was infiltrated with lymphocytes. A profound reaction of both microglia and swollen astrocytes was present in every area of Ammon's horn, and was most intense in Sommer's sector where all of the nerve cells were absent. Elsewhere, many of the nerve cells had disappeared also. The leptomeninges were infiltrated with scavenger cells, which were occasionally vacuolated. Meningeal hemorrhage was present in patchy areas; hemosiderin phagocytes were few. Several sections through the firm clot about the anterior cerebral artery showed a laminated unorganized thrombus. Only a fragment of the arterial wall was present, and the disrupted margins of the vessel were necrotic where they blended with the thrombus.

Extracortical gray matter: The globus pallidus exhibited focal necrosis with many gitter cells, glial stars, proliferated capillaries, and perivascular hemorrhages. Elsewhere, the small nerve cells showed chromatolysis. Many of the large cells exhibited margination of the Nissl bodies; a few showed satellitosis or neuronophagia. A diffuse proliferation of oligodendroglia and microglial cells with visible branched processes were also present. In comparison with the globus pallidus, the putamen exhibited somewhat less degeneration of nerve cells and glial reaction. However, occasional patches of necrosis, small glial nodules, and diffuse overgrowths of astrocytes, microglia, and rod cells were noted (figure 3). The caudate nucleus was similar. Glial stars and a diffuse gliosis were present in the thalamus. Some ghost cells were observed, and the cytoplasm of others was dark, often finely vacuolated, and sometimes contained lipoid pigment.

Cerebellum: Circumscribed areas of the cortex exhibited complete loss of Purkinje cells and a severe reduction to total loss of the cells of the granular layer. The molecular layer

was normally thick and contained proliferations of shrubbery glia and dense glial masses, which were oriented at right angles to the outer surface (figure 4). Within the glial masses were a few spicules of calcium. Because of the disappearance of the Purkinje and granular layers, the radially arranged glial growth of the molecular layer was in direct contact with the white matter. The slightly fibrotic leptomeninges contained a few erythrocytes and phagocytized hemosiderin. Elsewhere the cerebellar cortex showed a scattered outfalling of Purkinje cells, and some of those which remained were swollen and had diminished chromatin. The Bergmann cell layer was edematous, particularly at the apex of the convolutions, and it showed prominent gliosis. Throughout the cortex, the molecular layer also showed a mild diffuse gliosis, mainly with spidery or rod-shaped microglia, and the capillaries were numerically increased. The granular layer was intact. All of the white matter exhibited increased microglia, a few gitter cells, oligodendroglia, and rare small multinucleated giant cell nodules. The nerve cells of the dentate nucleus were numerically normal, but many showed severe nerve cell change.

Pons: Dense polypoid and flat mat-like masses of glial cells proliferated in the periventricular tissue and mushroomed into the fourth ventricle (figure 5). These granulomatous nodules contained multinucleated giant cells, many lymphocytes, and some polymorphs. A subependymal microglial reaction bordered the fourth ventricle and the aqueduct. The walls of the blood vessels in this region were infiltrated with lymphocytes and a few polymorphs. Mild degenerative nerve cell changes were noted throughout the pons. A small giant cell-glial nodule which contained fused columns and clumps of epithelioid cells was present in the pontile nuclei.

Medulla: The most striking feature was a diffuse gliosis, which was heaviest in the reticular substance. Many of the nerve cells in the reticular substance were extremely pale, and an occasional one showed neuronophagia. The cells of the inferior olivary nucleus were hyperchromatic.

Spinal cord: Fresh meningeal hemorrhage was severe. The motor nerve cells appeared normal. An increased number of glial cells was present in the posterior horns and throughout the white matter. Stains for fat and myelin revealed no degeneration of the nerve tracts.

Case 2.—A 72 year old white man had tic douloureux for two years. A craniotomy was performed using Avertin (85 mg./kg.) and ether anesthesia. The preoperative medication was morphine sulfate (gr. ¼) and atropine sulfate (gr. 1/150). The root of the trigeminal nerve was partially sectioned through an approach into the posterior cranial fossa. One half hour after the induction of the ether anesthesia, the blood pressure, which had been 150/110 preoperatively, fell to 80/55, but rose again within ten minutes to 160/120. Respiratory disturbances and cyanosis were not noted. Following operation the patient was comatose, and he never regained consciousness. At all times the muscles of the neck, trunk and extremities were flaccid. The pupillary and tendon reflexes were normal. Ankle clonus and atypical plantar reflexes were elicited. Although he appeared well oxygenated, he was given oxygen inhalations every two hours. From the second through the fourth postoperative days the spinal fluid was bloody but under normal pressure. On the fifth day the craniotomy wound was reopened, but no brain lesions were found which might have accounted for the coma. On the next day the rectal temperature rose to 103° F., and it continued high until his death on the twentieth day after the original craniotomy. No significant abnormal laboratory findings were present.

AUTOPSY

The body was well developed and well nourished. The heart weighed 340 gm. and appeared normal. The coronary arteries were widely patent. Multiple small bilateral pulmonary emboli and a small lung infarct were present. The liver exhibited a slight degree of fatty infiltration. Renal arteriosclerosis was slight.

Brain: The craniotomy wound extended from the right mastoid bone horizontally to the midline posteriorly. A round defect in the underlying bone, 2 cm. in diameter,

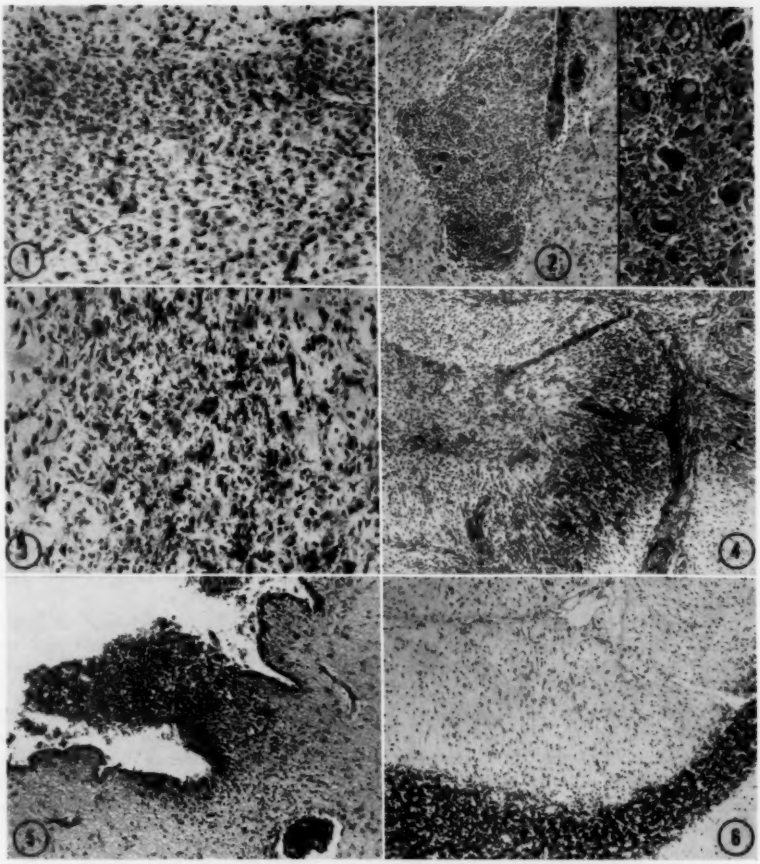

FIG. 1. Necrosis of cerebral white matter, showing proliferated gitter cells. *Case 1.* Nissl stain. FIG. 2. Multinucleated giant cell granuloma in cerebral cortex. *Case 1.* Nissl stain. High power field at right. FIG. 3. Focal necrosis of the putamen, showing neuronophagia, swollen astrocytes, and proliferated microglial cells. *Case 1.* Nissl stain. FIG. 4. Massive gliosis of the molecular layer of the cerebellum; absence of Purkinje cells and the granular layer. *Case 1.* Nissl stain. FIG. 5. Granuloma with giant cell projecting from pons into fourth ventricle. *Case 1.* Nissl stain. FIG. 6. Shrubbery gliosis of the molecular layer of the cerebellum and absence of Purkinje cells. *Case 2.* Nissl stain.

opened into the posterior cranial fossa. The inner surface of the dura mater and the arachnoid membrane immediately surrounding the wound contained several small recent and older hemorrhages. The embalmed brain weighed 1520 gm. The leptomeninges, except at the margin of the wound, were delicate, and over the right frontal lobe they showed a light yellow discoloration. The brain itself was firm. The cerebral cortex and inner nuclear masses did not appear remarkable. The brain tissue near the site of the operative

wound also appeared normal. The root of the right trigeminal nerve was partially transected and coagulated. No intracerebral hemorrhage was present. The intracranial vessels were delicate, presenting no evidence of arteriosclerosis or thrombosis. After fixation, one area of the left frontal cortex was slightly softer and less distinctly demarcated than the cortex elsewhere.

Cerebrum: Microscopically, destruction of nerve cells was widespread in the frontal lobes, particularly in the slightly softened area of the left frontal cortex. In this region the nerve cells had disappeared except in isolated instances. The field was dominated by the presence of innumerable rod cells and gemistocytic astrocytes. In addition, there was a growth of capillary endothelium and proliferation of many gitter cells. Several small collections of gitter cells were also present in the convolutional white matter. The deep white matter of the frontal lobes showed a generalized increase of protoplasmic astrocytes and a few small circumscribed perivascular areas of demyelinization, unaccompanied by a glial cell response. The adjacent leptomeninx contained several granules of calcium and a single calcified arteriole. The pial vessels otherwise showed no sclerosis. Elsewhere the cortex was decidedly poor in nerve cells, but the laminar architecture was not greatly altered, although some small, poorly delimited areas were devoid of nerve cells. Moderate numbers of ghost cells were present, and many cells showed either severe or ischemic cell changes. In general, the Nissl substance was scanty and the nerve cells were pale. Some of the cells were shrunken and had long, slightly twisted cell processes. Most of the nuclei were round, although some were triangular. The nucleoli were frequently fragmented and granular. In a few instances pericellular basophilic granular encrustations were seen. Most of the better preserved cells contained fine lipoid droplets. In areas other than the frontal lobe, the proliferation of rod cells and astrocytes was slight, except in the deepest layers where microgliosis and neuronophagia were prominent. A short segment of Sommer's sector of Ammon's horn was devoid of nerve cells. Neuronophagia, a diffuse outfalling of cells, and marked paling and shrinkage of the other cells were present elsewhere.

Extracortical gray matter: The lenticular nuclei and the thalamus showed moderate neuronal changes consisting of paling of the cells, crumpling of the nuclei, and pigment atrophy. Numerically, they were not significantly reduced. A diffuse gliosis was noted, particularly in the thalamus.

Cerebellum: A rather large number of Purkinje cells were absent, but those remaining stained well. Large foci of shrubbery glia were present in the molecular layer in several of the convolutions (figure 6). In other convolutions a slight to moderate diffuse proliferation of rod-shaped cells was present throughout this layer. The dentate nucleus showed occasional ghost cells, neuronophagia, and a diffuse heavy proliferation of oligodendroglia and microglia. Glial stars were numerous in the white matter.

Pons and medulla: The pontile nuclei in all areas exhibited mild to moderate degenerative changes similar to the neurons of the cortex. The medulla, especially beneath the fourth ventricle, contained many minute glial nodules and showed some neuronal destruction. Most of the cells of the inferior olivary nucleus showed advanced pigment atrophy; others showed vacuolation or sclerosis.

Case 3.—A 33 year old negro woman had a panhysterectomy for uterine leiomyomas and chronic pelvic inflammatory disease. The preoperative blood count showed a hemoglobin level of 9.9 gm. and 4,080,000 erythrocytes. Following a transfusion (500 cc. of whole blood), she was given preoperative medication of morphine sulfate (gr. ¼) and atropine sulfate (gr. 1/150). Ether was administered by closed system after induction with cyclopropane. Another 500 cc. of blood was given during the operation. The operation was well tolerated and lasted two hours and 45 minutes. The patient failed to regain consciousness following surgery. Respirations were 20 per minute, the pulse rate was 80, and the blood pressure was 130/87. Twelve hours later she was unexplainedly given ¼ gr. of morphine, and the respiratory rate fell to six per minute, remaining at that level

until she died after another six hours. She never had convulsions nor exhibited focal neurologic signs.

AUTOPSY

The body was well developed and well nourished. An incision extended from the umbilicus to the symphysis pubis. The uterus and adnexa were absent. Diffuse hemorrhage was present in the pelvic connective tissue, but no blood was free in the abdominal cavity. The heart weighed 270 gm., and the ventricles were contracted. The coronary arteries were thin-walled and widely patent. The lungs exhibited slight edema. The kidneys were normal.

Brain: The embalmed brain weighed 1220 gm. The cerebral cortex and the brain stem appeared normal. A few minute hemorrhagic spots were present in the white matter which bordered the lateral ventricles. An area of the cerebellar cortex occupying the basal aspect of the left hemisphere, which measured 3.5 cm. in diameter, was softened, fragmented, and anemic. The arteries showed no sclerosis nor obstruction.

Cerebrum: Microscopically, numerous nerve cells throughout all layers of the cortex showed degenerative changes. Some cells were swollen, and the chromatin was clumped at the periphery. The nuclei were oval and pale, and the nucleoli were eccentric or absent. Many other cells exhibited advanced chromatolysis; they were shrunken and distorted and had indistinct cell membranes. Many cells remained as finely stippled husks without Nissl bodies or nuclei. These changes were observed in all areas, but were slightly more prominent in the parietal lobe, where there also was an outfall of Betz cells. Glial proliferation was slight. The white matter contained an unusually large number of swollen oligodendroglial cells. Demyelinization was not observed. In Ammon's horn a few cells of Sommer's sector were absent. Both the large cells and small cells of the lenticular nuclei showed degeneration similar to that of the cerebral cortex. The thalamus appeared identical.

Cerebellum: In the areas of gross softening, the Purkinje cells were acidophilic or "hyaline." The granular layer was swollen, and in large areas the cells were absent. Elsewhere most of the Purkinje cells showed complete chromatolysis and possessed round pyknotic nuclei. Others stained a solid dark blue, and the nuclei were overshadowed. Some cells were encrusted with dark blue granules. Focal areas of Bergmann's cell layer were edematous, slightly infiltrated with polymorphs, and slightly thickened by an early glial reaction. The dentate nucleus showed a spotty outfalling of nerve cells, foci of severe nerve cell change, and slight focal infiltration with polymorphs. Throughout the white matter there were increased numbers of oligodendroglia cells and astrocytes. The Scharlach-R stain revealed no neutral fat.

Pons and medulla: Throughout the nuclei of the pons and medulla, numerous nerve cells exhibited the same changes as those of the cerebral cortex and basal nuclei; swelling, pyknosis, chromatolysis, and shrinkage. Large patches of the inferior olivary nuclei were devoid of nerve cells. A slight diffuse gliosis was present.

DISCUSSION

The brain damage in these cases was considered to be the result of an unusual reaction to ether, since episodes of anoxia were not detected during surgery. The devastating train of events in case 1 was set off by the anesthetic. The rupture of the cerebral aneurysm occurred only a few days before death, judging from the spinal fluid findings and the gross appearance of the brain. A renal vasomotor reaction may have been responsible for the anuria, which was followed by pyelonephritis, uremia, hypertension, and cardiac hypertrophy. Damage to the respiratory center, resulting in excessive loss of carbon dioxide from the lungs, was probably the explanation for the sustained alkalosis coincident with the uremia. In case 2, a transient fall in blood pres-

sure during the operation may have been important, although the severity of the drop was not unusual. Cerebral vascular disease was not a factor. Moderate anemia may have been significant in case 3; a dose of morphine probably contributed to death, but the coma appeared to have been already established.

The cerebellum was the most consistently vulnerable area of the brain. Typical anemic infarction occurred in the case of shortest coma. With prolonged coma, diffuse shrubbery gliosis of the molecular layer, the formation of dense glial masses, and loss of Purkinje cells were outstanding features. The earliest cerebral change consisted of widespread degeneration of the nerve cells throughout the cerebral cortex and the inner nuclear masses. The laminar structure of the cortex was rarely affected. Only in case 2 was actual cortical necrosis present, and it was confined to one frontal lobe. Although some areas of the cortex were affected more than others, in general the changes were diffuse, and sites of predilection were not determined. The cortical gliosis was widspread, but in the main quite moderate. Disappearance of the nerve cells of Ammon's horn was proportionately severe to the duration of coma. The nerve cell changes in the basal nuclei were severe. In case 3, where coma was brief, neuronal changes were about equal in the cortex, basal nuclei, and medulla. The severity of nerve cell degeneration and gliosis in the basal ganglia exceeded that of the cortex in the case of longest coma. In this case, also, necrosis of the cerebral white matter was advanced and symmetrical. Associated with necrosis were numerous giant cell granulomas, located predominantly in the cortex, and granulomatous glial growths from the ependyma into the lumen of the fourth ventricle. Degeneration of the white matter was a minor feature in case 2, and consisted of small perivascular foci of demyelinization.

Necrosis of the white matter was not considered to be a specific reaction to ether. This lesion was more likely related to the severity of the initial insult, to cerebral edema, and to prolongation of the comatose state. Hurst[10] demonstrated that demyelinization of the white matter might occur under certain circumstances without concomitant cortical damage. Repeated doses of potassium cyanide, which were not large enough to affect the cerebral cortex, produced demyelinization in monkeys. Morrison[11] subjected monkeys to low barometric pressures and produced different cerebral lesions by varying the intensity of the insult. Mild exposures caused degeneration of the cortical nerve cells, while sudden single exposures resulted in laminar necrosis of the cortex. Repeated severe exposures caused widespread demyelinization which in the severest cases resembled Schilder's disease. Neubuerger and Clarke[12] reported a similar case of coma of 14 days' duration in a 19 year old girl who had been exposed to carbon monoxide. Instead of exhibiting the more common lesion of necrosis of the globus pallidus, the cerebral white matter showed extensive degeneration. The authors believed that the anoxemia produced by the carbon monoxide caused a vasomotor disturbance which resulted in the myelinopathy. They also stated that diffuse myelinopathy had

been described as a consequence of cerebral edema, which may be present in anoxemic states. Seldon and his associates[13] reported the case of a 27 year old woman who was in coma for 21 days after ether anesthesia. She recovered following therapy with 25 per cent human serum albumin, which was administered with the intention of relieving cerebral edema. They regarded permanent damage to the brain as a function not only of the acute anoxic episode, but also of periods of sublethal anoxia and postanoxic cerebral edema.

Multinucleated giant cells are rarely found in the brain. Ferraro[14] collected 12 cases from the literature in which giant cells were observed. All were associated with demyelinating diseases. Most of the authors believed that the giant cells originated from glial cells, although in one instance they appeared to be derived from adventitial cells. Ferraro produced perivascular demyelinization and multinucleated giant cells in monkeys by multiple injections of an alcoholic antigenic brain extract. The presence of the cells about blood vessels remote from the areas of damaged myelin was noted. He believed that giant cells and granulomatous reactions were integral though not constant features of the early stages of demyelinating diseases. In the case of postanesthetic myelinopathy, the most likely explanation for the giant cell granulomas was that they represented a response to the action of antigenic substances derived from the degenerating myelin.

A comparison of the cerebral lesions which followed ether anesthesia with those observed in other anoxic states is necessary, but a detailed review of the literature is not attempted. The summary by Courville[2] serves to show that sites of predilection differ with the agent. Damage to the cerebral cortex was most constant in nitrous oxide anesthesia, and changes in the globus pallidus were variable. The reverse was true in carbon monoxide poisoning. Cyclopropane was similar to nitrous oxide. Cortical alterations of less severe degree occurred with spinal anesthesia, and lesions of the globus pallidus were present. In a case of ethylene anesthesia, changes consisted of a diffuse minor softening of the cortex followed by a generalized reaction of the capillaries. Titrud and Haymaker[15] published two cases of coma due to high altitude asphyxia. Duration of the coma was 40 hours in one case and three weeks in the other. Conspicuous necrosis of nerve cells was observed in the cerebral cortical layers three to six, in the corpus striatum, and in Ammon's horn. The Purkinje cells showed some destruction. In the case of longer coma, the external portion of the globus pallidus was necrotic, and areas of the molecular layer of the cerebellum exhibited a proliferation of glial cells. A case of coma for 26 days after the occurrence of cardiac arrest under a mixture of anesthetics was reported by Hawkins, McLaughlin and Daniel.[16] Extensive necrosis and gliosis were present in the cerebral cortex and basal nuclei. Some of the Purkinje cells were absent, and varying degrees of gliosis were present in the molecular layer of the cerebellum. In an extensive review of anoxia from many causes, including anesthetics, Hoff, Grenell and Fulton[17] concluded that anoxia itself was only one factor in the production of neuronal lesions. Complex metabolic factors of cellular oxidative processes, physicochemical re-

actions, and the number and pattern of blood vessels in different areas of the brain were all factors of varying importance in diverse anoxic conditions.

How ether acts to produce anoxic lesions is an important consideration. The roles of allergy, idiosyncrasy, anoxemia, and direct action on the enzyme system of nerve cells are difficult to evaluate. Stein[18] reported the only proved case of allergy to ether; circulatory collapse occurred without neurologic symptoms. Ether convulsions, which are evidence of cerebral injury, were considered to be a manifestation of idiosyncrasy by Hadfield.[19] Ray and Marshall,[20] however, favored anoxia rather than special susceptibility as the chief cause of convulsions; several of their patients who had anesthetic convulsions did not have them at prior or subsequent surgery. Williams and Sweet[21] believed a constitutional factor was important in ether convulsions. About three quarters of a group of 22 patients who had convulsions exhibited abnormal electroencephalograms, which were not different from those of epileptics. Lundy[22] tabulated numerous possible causes of anesthetic convulsions, and these included toxemia, carbon dioxide excess, overdosage of atropine, heat, youth, etc. Courville[2] pointed out that most of these factors bore a relationship to disturbed tissue respiration. In the case of ether, disturbance of oxidation was not due to diminished oxygen in the circulating blood, alteration of the oxygen-carbon dioxide exchange in the blood stream, nor to circulatory stagnation. The narcotic effect of ether was the result of interference with gaseous exchange through the nerve cell membrane or within the cytoplasm. It is not unreasonable to assume that ether may cause a histotoxic type of anoxia.

In summary, the term anoxia ought not to be used loosely in connection with the pathogenesis of cerebral lesions attending the use of ether. Nevertheless, average doses of ether apparently caused anoxia of critical degree at the nerve cell level. The evidence indicates that some patients show an unusual susceptibility to ether, and that its use probably carries the danger of leaving the patient with residual brain damage as well as causing fatal reactions. The pattern of cerebral lesions associated with ether death differs somewhat from the brain changes which result from other anesthetics and occur in other anoxic states. The character of the lesions, however, is probably as much the result of vasomotor disturbances, cerebral edema, and prolongation of coma as of the specific nature of the anesthetic agent.

SUMMARY

The cerebral lesions observed in three cases of coma of from 18 hours to 35 days following ether anesthesia are described. The cerebellum was the most consistently damaged area of the brain; anemic infarction, loss of Purkinje cells, and severe gliosis of the molecular layer occurred. Neuronal degeneration in the cerebral cortex was most extensive in the patient who survived the shortest time. Actual cortical necrosis was present focally in one patient. Degeneration of the basal nuclei was similar, on the whole, to that of the cerebral cortex. In the case of most prolonged coma, the cerebral white matter exhibited advanced symmetrical necrosis. Associated with this lesion

were multiple multinucleated giant cell granulomas throughout the cerebral cortex and projecting into the fourth ventricle. Anoxemia or circulatory stagnation did not appear to be major factors in the production of the cerebral damage. The character of the lesions probably depended not only on the specific nature of the anesthetic, but also on cerebral vasomotor disturbances, cerebral edema, and the duration of coma.

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Tissot says—"Migraine is distinguished by the severity of the pain, by a kind of periodical return, by the similarity of different attacks, by its recurrence independently of those accidental causes which determine other kinds of headache. We may say generally of every seizure that its onset is spontaneous and somewhat sudden, sometimes with a slight sense of chilliness, and then the paroxysm is often more violent; the pain, however, does not set in at first in its full severity, which it does not usually attain for an hour and a half, and then remains at the same intensity for some hours."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Preliminary Studies of Sludged Blood in Multiple Sclerosis

Leon Roizin, M.D., R. C. Abell, M.D. and J. Winn, M.D.

FROM Rindfleisch[1] and Ribbert[2] up to the present time many investigators have advanced hypotheses regarding various aspects of the vascular mechanisms[3–9] and some of the biochemical blood abnormalities[10–13] in the pathogenesis of the lesions of multiple sclerosis. There is not, however, complete agreement among these investigators. Recent studies have established the fact that the rate of blood flow through the tissues is determined by the maximal rate at which the cells absorb metabolic material carried in the blood. Among the latter, oxygen is one of the most important anabolites. Even slight local oxygen deficits are known to initiate or precipitate metabolic or functional disorders which, if perpetuated, may eventually lead to reversible or irreversible pathologic alterations.

Among various local or general pathogenetic mechanisms, sludged blood was considered worthy of exploration in view of the fact that sludge might interfere with certain dynamic and biochemical aspects of the circulatory mechanisms. It was felt that a study of the blood as seen with the microscope in the vessels of a selected group of cases of multiple sclerosis might help to determine (a) whether sludge is in fact present in the course of multiple sclerosis, (b) whether sludge, if present, is of significance as an etiologic factor, and (c) whether its presence is related to the above-mentioned vascular and biochemical abnormalities.

MATERIAL AND METHODS

Up to the present time 24 selected patients suffering from multiple sclerosis have been studied. The fundamental clinical features of these cases are briefly summarized in table 1. The patients were examined frequently and studied ambulatorily for a period of approximately four to seven years. During this period of time they were subjected to various standard laboratory

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TABLE 1
SUMMARY OF THE PRINCIPAL CLINICAL FEATURES OF 24 MULTIPLE SCLEROSIS CASES.

Pts. No.	*Sex & age*		*Predominant ctinical symptomatology*	*Clinical Character*	*Course of illness*	*Duration (years)*	*Remarks*
1	M	30	Generalized	Mild, ambulatory	Unstable	5½	Occasionally mild relapses
2	M	29	Generalized	Severe, wheelchair	Progressively worse	7	Occasional moderate relapses
3	M	40	Generalized	Severe, wheelchair	Stable	6+	Trophic changes
4	M	30	Generalized	Severe, wheelchair	Progressively worse	6+	Marked mental deterioration
5	M	27	Generalized	Mild, ambulatory	Slightly unstable	7+	Unchanged
6	M	26	Generalized	Mild, ambulatory	Slightly unstable	6	Psychopathic personality
7	M	28	Spastic, paraplegia	Moderate, wheelchair	Stable	6	Occasionally some improvement
8	M	32	Generalized	Mild, ambulatory	Slightly unstable	6	Unchanged
9	M	40	Generalized	Moderate, ambulatory	Unstable	6+	Progressively worse
10	M	30	Generalized	Moderate, ambulatory	Unstable	6+	Duodenal ulcers, unchanged
11	M	32	Generalized	Moderate, ambulatory	Unstable	7	Unchanged
12	M	35	Hemiparesis	Mild, ambulatory	Stable	6+	Unchanged
13	M	36	Generalized	Moderate, wheelchair	Unstable	6+	Slightly worse
14	M	29	Paraparesis	Mild, ambulatory	Unstable	5+	Slightly worse
15	M	30	Generalized	Severe, wheelchair	Progressively worse	8+	Trophic changes
16	M	30	Generalized	Severe, wheelchair	Unstable	5+	Progressively worse
17	M	32	Generalized	Moderate, ambulatory	Unstable	6	Progressively worse
18	M	30	Generalized	Severe, wheelchair	Unstable	5+	Progressively worse
19	M	33	Generalized	Mild, ambulatory	Unstable	4½	Unchanged
20	F	30	Generalized	Severe, wheelchair	Unstable	6+	Occasionally some improvement
21	M	30	Generalized	Moderate, ambulatory	Unstable	8+	Slightly worse
22	M	29	Generalized	Moderate, ambulatory	Unstable	6	Slightly worse
23	M	28	Generalized	Moderate, wheelchair	Unstable	6+	Duodenal ulcer, worse
24	M	32	Generalized	Moderate, ambulatory	Unstable	7	Progressively worse

tests (table 2) which did not reveal any definitely abnormal processes in their blood hematology. In addition, all the patients during that period of time were maintained on a standardized regimen of life and on an adequate diet. The blood was investigated for sludge in these selected cases during two periods of time: the first series of observations was made in 1950 and the second series in 1951, approximately ten to 12 months later.

The behavior of the blood cells and their flow through the small vessels

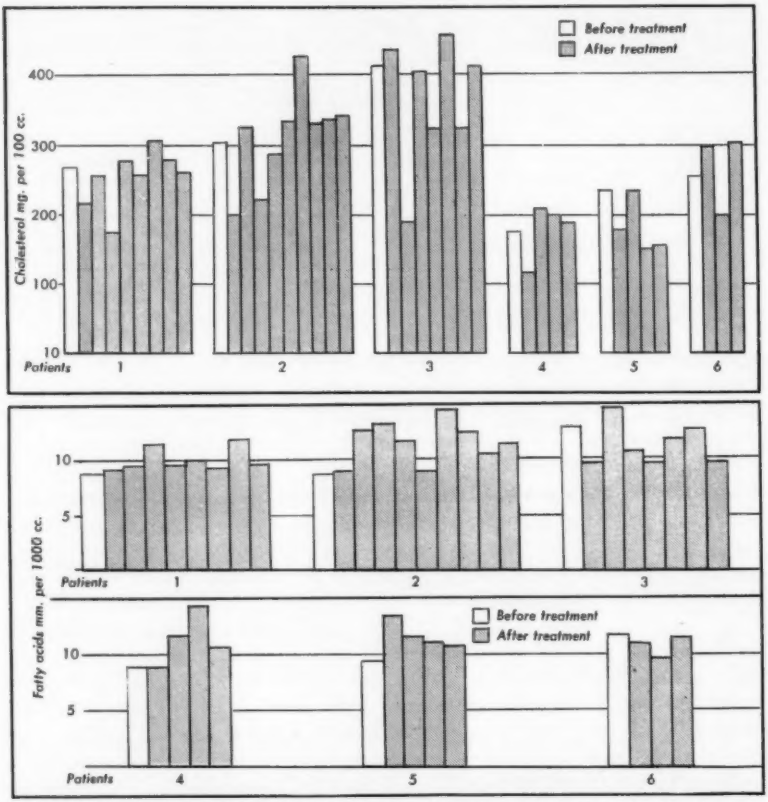

FIG. 1. *(above)* Blood cholesterol levels in a sample of six multiple sclerosis patients taken at random from the 24 patients studied. Unshaded columns indicate the level of cholesterol in mg. per 100 cc. of blood, determined before vitamin therapy (B_1, B complex, and ascorbic acid) was initiated. Shaded columns indicate the levels of cholesterol taken at various intervals of time after the first one.

FIG. 2. *(below)* Fatty acid levels in a sample of six multiple sclerosis patients taken at random from the 24 cases studied. Unshaded columns indicate the level of the fatty acids in mg. per 1000 cc. of blood before vitamin therapy was initiated. Shaded columns indicate the levels of fatty acids taken at various intervals after the first one.

were studied in the bulbar conjunctiva, using a technique described by Knisely and associates.[14] This consisted of observing the blood vessels and blood cells with a slit lamp, using oblique illumination. The present studies were made at magnifications of 31x and 47x.

Control observations were made using 20 apparently healthy individuals comparable in age to the patients with multiple sclerosis. In addition to the above-mentioned standard laboratory examinations, additional blood studies were performed concomitantly, as shown in figures 1 and 2, inasmuch as such

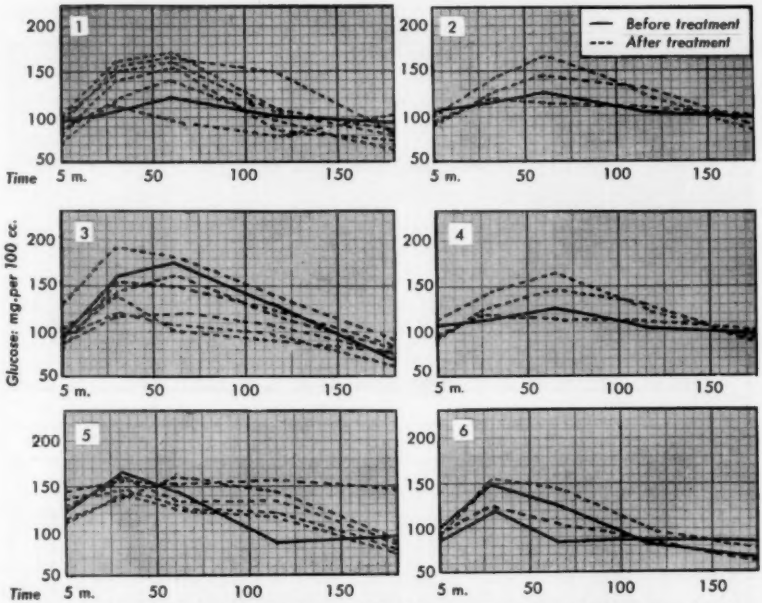

FIG. 3. Glucose levels in a sample of six multiple sclerosis patients taken at random from the 24 cases studied. Solid lines indicate the glucose levels in mg. per 100 cc. of blood before vitamin therapy (B_1, B complex, and ascorbic acid) was initiated. Broken lines indicate the glucose levels taken at various intervals after the first one.

studies have been considered by certain investigators[12] to be important in demonstrating some of the abnormal metabolic processes which, at times, have been observed in various demyelinating diseases. In addition, glucose tolerance tests were performed (figure 3) and prothrombin levels determined (figure 4) for the purpose of detecting possible liver labilities.

CLINICAL FINDINGS

For the sake of simplicity and clarity, the patients are numbered from one to 24. The essential clinical findings are summarized in table 3.

The amount of sludge present in the blood is shown in figure 5, and is graded as follows: grade O – no sludge was observed; grade 1 – sludge present to a slight degree; grade 2 – sludge present to a moderate degree; grade 3 – sludge present to a marked degree; grade 4 – sludge present to a very marked degree; grade 5 – the stage at which a lump of sludge has stuck in a vessel and has stopped the blood flow. Grade 5 was observed in only two patients in the present study. All gradations of sludge were made by a single trained observer.

Of the total number of 24 multiple sclerosis patients studied, 13 were investigated in both series. Of the 19 patients in the first series, sludge was seen

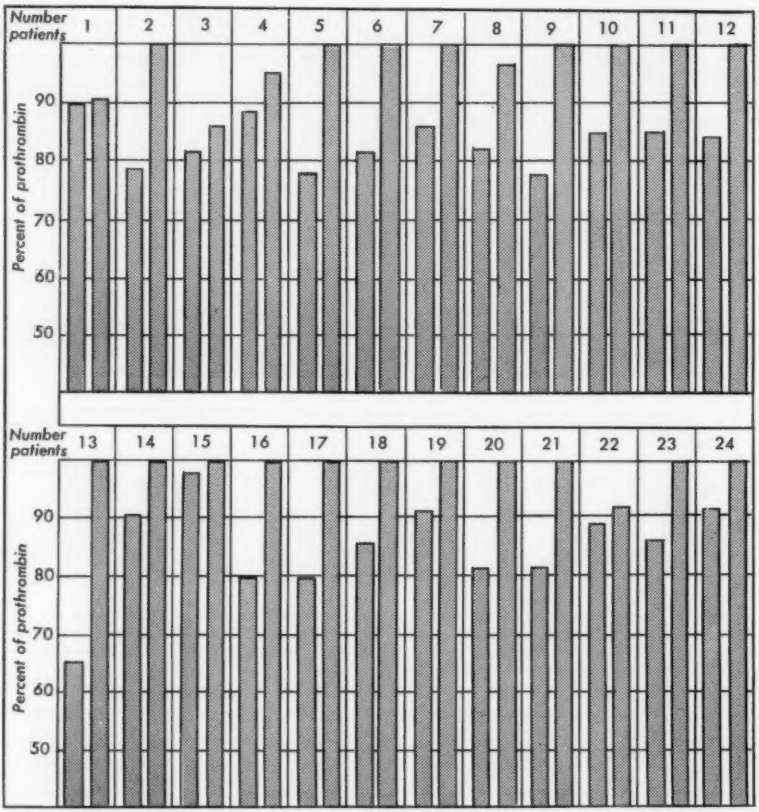

FIG. 4. Prothrombin levels of the individual 24 multiple sclerosis patients studied. The left column for each patient indicates the average percentage of the lowest level of prothrombin (obtained from a large number of determinations) and the right column indicates the average percentage of the highest level of prothrombin (obtained from a large number of determinations).

in 13. The fact that it was not detected in six of the patients may have been due to the low magnification used (31x), which was the highest available at that time. The amount of sludge seen in the 14 positive cases was as follows: grade 1 in one patient, grade 2 in nine patients, grade 3 in one patient, and grade 4 in three patients. Of the 18 patients studied in the second series, sludge was observed in all instances, the amount being as follows: grade 2 in four patients, grade 3 in eight patients, and grade 4 in six patients. The magnification used in this latter series was 47x (compared to 31x in the first series), and it may be because of this higher magnification that sludge was detected in all cases of this second series.

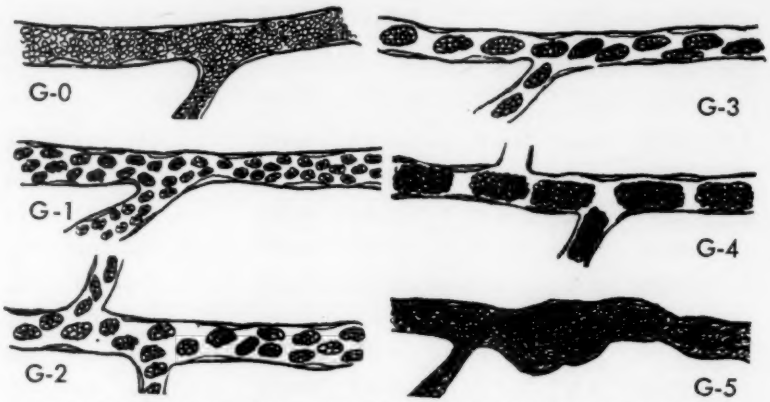

FIG. 5. Schematic drawings of the various degrees of sludged blood within the bulbar conjunctival blood vessels as explained in the text.

In nine of the cases studied in both series there was an increase in the amount of sludge during the ten to 12 month period separating the observations. In four of the patients the same amount of sludge was present both times; no decrease occurred in any of the patients. These findings suggest that as the disease progressed in the above-mentioned nine cases, so did the amount of sludge. However, in view of the limited number of such cases observed in the present studies, further observations are required before any final conclusion can be reached. In two of the cases (patients 21 and 24) masses of sludge were observed acting as emboli which completely blocked the circulation in two small areas of the conjunctiva in one patient and in one area in the other (figure 5, G-5).

Concomitant blood studies, in summary, have disclosed the following findings.

1. Blood hematology as indicated in table 2 did not reveal any marked abnormality with the exception of patients 2, 6, 11, 19, and 20, who showed temporary increases in the leukocytes, which during subsequent examinations have returned to a more or less normal average.

2. The sedimentation rate (table 2) appeared variable in character and reached a higher level in only seven patients (5, 8, 15, 18, 19, 20, and 22).

3. Blood cholesterol determinations (figure 1) disclosed variations not only among the various cases but also in the same case at various periods of time. Only in some cases (figure 1, groups 1, 2, 3, and 6) the cholesterol appeared higher (oscillations between 200 and 470 mg. per 100 cc. of blood). However, this increased cholesterolemia was generally temporary in character inasmuch as it was alternated by lower levels.

4. The blood fatty acid examinations (figure 2) did not disclose any significant or lasting abnormalities.

TABLE 2

SUMMARY OF BLOOD HEMATOLOGY IN MULTIPLE SCLEROSIS PATIENTS.

Pts. No.	*R.B.C.*	*Hb*	*Leukocytes*	*Platelets*	*Sed. rate*	*Color*	*W.K. I. Tests*
			8.000				
1	4.200.000	13.4g	N:56 E:1 B:1 L:42 M:0	200.000	6 mm./1 hr.	0.9	Neg.
			19.200				
2	5.020.000	13.0g	N:71 E:1 B:1 L:22 M:5	240.000	2 mm./1 hr.	0.76	Neg.
			6.800				
3	4.750.000	12.5g	N:46 E:1 B:1 L:51 M:1	200.000	4 mm./1 hr.	0.77	Neg.
			9.200				
4	5.000.000	14.5g	N:69 E:5 B:0 L:25 M:1	250.000	11 mm./1 hr.	0.85	Neg.
			9.600				
5	4.700.000	15.5g	N:73 E:0 B:0 L:24 M:3	250.000	23 mm./1 hr.	0.9	Neg.
			12.800				
6	4.850.000	13.0g	N:65 E:3 B:0 L:32 M:0	200.000	4 mm./1 hr.	0.79	Neg.
			7.600				
7	4.950.000	15.5g	N:66 E:1 B:0 L:31 M:2	230.000	5 mm./1 hr.	0.94	Neg.
			7.400				
8	4.250.000	12.5g	N:65 E:2 B:0 L:30 M:3	270.000	14 mm./1 hr.	0.87	Neg.
			8.300				
9	4.430.000	15.3g	N:54 E:1 B:0 L:40 M:5	210.000	3 mm./1 hr.	1.02	Neg.
			8.500				
10	4.650.000	15.5g	N:42 E:0 B:0 L:57 M:1	230.000	5 mm./1 hr.	0.9	Neg.
			12.500				
11	5.050.000	16.0g	N:74 E:2 B:0 L:23 M:1	290.000	8 mm./1 hr.	0.9	Neg.
			8.000				
12	4.920.000	16.8g	N:53 E:2 B:0 L:37 M:4	210.000	2 mm./1 hr.	1.0	Neg.
			5.950				
13	4.650.000	13.4g	N:62 E:4 B:0 L:33 M:1	290.000	10 mm./1 hr.	0.86	Neg.
			8.500				
14	4.250.000	15.0g	N:67 E:2 B:0 L:29 M:2	210.000	10 mm./1 hr.	1.0	Neg.
			8.100				
15	4.720.000	13.0g	N:53 E:2 B:2 L:40 M:3	200.000	13 mm./1 hr.	0.81	Neg.
			8.100				
16	4.990.000	12.0g	N:66 E:0 B:2 L:3 M:1	340.000	5 mm./1 hr.	0.71	Neg.
			5.200				
17	5.050.000	14.5g	N:61 E:1 B:0 L:38 M:0	200.000	3 mm./1 hr.	0.85	Neg.
			7.600				
18	4.850.000	13.9g	N:50 E:8 B:0 L:41 M:2	230.000	17 mm./1 hr.	0.85	Neg.
			11.100				
19	4.200.000	15.0g	N:76 E:1 B:0 L:20 M:3	250.000	17 mm./1 hr.	1.04	Neg.
			9.600				
20	4.470.000	14.5g	N:59 E:1 B:1 L:37 M:2	190.000	15 mm./1 hr.	0.9	Neg.
			6.900				
21	4.790.000	13.4g	N:60 E:3 B:0 L:36 M:1	230.000	9 mm./1 hr.	0.85	Neg.
			6.900				
22	4.750.000	13.0g	N:62 E:0 B:0 L:32 M:6	220.000	18 mm./1 hr.	0.81	Neg.
			9.700				
23	4.200.000	17.0g	N:71 E:3 B:1 L:20 M:5	240.000	4 mm./1 hr.	1.0	Neg.
			5.400				
24	4.600.000	14.5g	N:66 E:2 B:0 L:29 M:3	210.000	15 mm./1 hr.	0.9	Neg.

REMARKS: Patient 1: Hypochromia, Microcytes, Poikilocytes
Patient 3: Slight hypochromia, Anisocytosis
Patient 6: Hypochromia, moderate anisocytosis, moderate microcytes
Patient 8: Reticulocyt. 1.5%
Patient 13: Slight hypochromia
Patient 15: Moderate hypochromia and anisocytosis
Patient 16: Reticulocyt. 1.9%, Moderate anisocytosis and hypochromia
Patient 21: Slight hypochromia and anisocytosis
Patient 22: Mild hypochromia and anicocytosis

TABLE 3
SUMMARY OF THE SLUDGED BLOOD EXAMINATIONS AS EXPLAINED IN THE TEXT.

PTS.NO.	FIRST SERIES OF PATIENTS		SECOND SERIES OF PATIENTS		REMARKS
	Grade of sludge	*Magnification*	*Grade of sludge*	*Magnification*	
1	0	31X		47X	
2	0	31X	3	47X	Increased
3			2	47X	
4	4	31X	4	47X	Same
5	2	31X	2	47X	Same
6			1 to 2	47X	
7	2	31X	3	47X	Increased
8	0	31X			
9			3	47X	
10	0?	31X			
11	4	31X	4	47X	Same
12			3	47X	
13	2	31X	2	47X	Same
14	2	31X			
15	2	31X	3	47X	Increased
16	2	31X	3	47X	Increased
17	2	31X	3	47X	Increased
18			4	47X	
19	2	31X			
20	1?	31X	4	47X	Increased
21	2	31X	4	47X	Increased
22	4	31X			
23	0?	31X	3	47X	Increased
24	3	31X	4	47X	Increased

5. No significant or persistent changes have been noticed in the glucose tolerance tests (figure 3) and prothrombin determinations (figure 4).

DISCUSSION

For a better understanding and evaluation of the possible effects of the sludged blood it is necessary to recall briefly some of the fundamental factors which regulate the physiology of the circulatory system: 1) the physico-chemical properties of the blood, 2) the dynamics of the blood flow, and 3) the morpho-functional role of the vessel walls.

1. In the present discussion the oxygen appears as one of the most important elements of the factors in this group. It is well established that oxygen a) is essential for the respiratory activity of any living tissue cell; b) is not stored as a free element in the tissues, and c) changes quantitatively as a result of necessary physiologic adjustment. Therefore, temporary or even slight decrease in oxygenation might lead to reversible disorders of a functional character or irreversible pathologic changes (if perpetuated over a long enough period of time). The latter phenomenon assumes particular importance in the present discussion because it is well known that the central nervous system is especially sensitive to even mild and temporary ischemia and anoxia.

2. The rate of blood flow through the tissues of each organ is regulated by the physiologic activity of the particular tissue. Apparently the rate of blood flow is such that it supplies the cells of the functioning tissue with the optimal amount of circulating nutrients.

3. Intimately connected with the process as described above, under 2, is the morpho-functional role of the vessel walls. It is generally known that the rate of blood flow through the tissues is regulated by the vasomotor reflexes. Therefore, the diameter of the vessels may remain approximately uniform under adequate and constant conditions or may change from time to time according to variations in functional activity of the tissues, oxygen supply, amount of circulating anabolites, catabolites, and so forth. Many of these reaction patterns, however, are very complex and to avoid unwarranted deviations from the main purpose of our discussion we would like to refer those who are interested in more detailed knowledge of this subject to Krogh,[15] Knisely,[14,16,17] and Clark.[18,19] Furthermore, in relation to the morphofunctional role of the vessel walls, it is worth mentioning that: 1) the capillaries which carry blood toward the tissues vary in size from a little less than one to as much as two and a half times the diameter of the circulating red cells, and 2) under both physiologic and abnormal conditions the capillaries act as a perpetual bottleneck in the vascular system.

Agglutinated corpuscle masses (sludge) can act as minute emboli which are capable of plugging small blood vessels and capillaries. Two such instances were clearly observed (patients 21 and 24 in the second series), as noted previously. Knisely states that "resistance of sludged blood to its own passage through the bottlenecks of the circulatory system forcibly reduces the rates of blood flow through all the open vessels" of that area. He states further that "various degrees of reduction in circulating blood volume 'might' initiate intermittent or prolonged shutting off of the blood vessels of a selected series of tissues and organs." The findings indicate the existence of such phenomena in a high percentage of the multiple sclerosis patients studied.

It appears probable, therefore, in accordance with the fundamental factors regulating the physiology of the circulatory system in the tissues, that sludge might cause a degree of ischemia or heterophasic tissue anoxia, which, if perpetuated for a prolonged period of time, could eventually induce more or less permanent or irreversible local histometabolic and, consequently, histopathologic changes.[20] That such changes, with actual plugging of the capillaries, are in fact produced by sludge in monkeys with Knowlesi malaria has been demonstrated with the utmost clarity by Knisely.[16] In this series of studies he also showed that when atabrine or quinine was given, the sludge disintegrated into individual red cells or clumps so small and soft or plastic that they did not resist passage through the small vessels and thus retard the blood flow. Following this the circulation became normal and the animals survived.

In a recent publication Fowler and Zeckel[21] showed that, in patients with Ménière's disease, clumping of red blood cells and sluggish flow in small vessels were present to a marked degree shortly before and after the Ménière attacks. Between attacks, sludging of the blood was decreased or absent. Furthermore, they were able to induce Ménière's attacks experimentally by psychic stimuli, and at such times observed the induction of sludge. In addition they found that intravenous administration of procaine altered or stopped

the tinnitus in several cases of Ménière's disease, and that concomitantly with this the sludge disappeared. They suggest that lumps of sludge, when caught in the smaller vessels of the labyrinth, are instrumental in the production of labyrinthine hydrops, which have been found to be characteristic of the pathology of the disease.

In the multiple sclerosis patients in the present studies it has not been possible to observe directly the flow and state of blood in the brain and nervous tissues. Consequently, sludge interfering with the blood flow in the nervous tissue itself has not been seen. However, as pointed out by Knisely, the blood in the conjunctival vessels is a valid sample of its condition elsewhere in the body. Consequently, there is reason to believe that when sludge is seen in bulbar conjunctival vessels, as observed in the multiple sclerosis cases studied, it is also present in the vessels which supply the cerebral spinal system.

The findings suggest that, in multiple sclerosis, lumps of sludge may plug capillaries supplying nervous tissue and thus seriously interfere with its blood supply. In this way sludge may be of pathogenetic significance in the development of the disease, since it has been clearly shown in the cases of malaria[16] and Ménière's disease[21] that disintegration of the sludge (which in malaria coincided with the destruction of the parasites) was followed by mitigation or disappearance of the symptoms. In view of these facts it is possible to speculate that if methods were found to disintegrate the sludge in multiple sclerosis prior to the production of irreversible pathologic changes, some of the symptoms of this disease might likewise be mitigated or their progressive course arrested. None of the chemical methods used in the present series were found to have any observable effect upon the sludge.

Since sludge may be a general reaction of some immunochemical nature,[22] and since vascular emboli have been shown to occur in allergic processes,[23] a study of the sludged blood in experimental allergic encephalomyelitis (produced with various central nervous tissue antigens) and allied demyelinating diseases is being planned.

SUMMARY AND CONCLUSIONS

1. The blood in the bulbar conjunctival vessels of 24 selected multiple sclerosis patients was examined for sludge at magnification of 31x and 47x. The patients were studied on two occasions, separated by an interval of ten to 12 months. In the first series of 19 patients, 13 showed sludge to a significant degree. In the second series of 18 patients, sludge was observed in all instances. In nine of the 13 patients studied in both series there was an increase in the amount of sludge in the interval of ten to 12 months separating the observations. These observations suggest that sludged blood might be considered as one of the pathogenetic factors underlying the fleeting symptoms or the insidious relapses so commonly observed in multiple sclerosis.

2. Thrombus-like formations caused by sludge were observed in the vessels in two of the multiple sclerosis patients. It is postulated that the thrombosis of blood vessels in multiple sclerosis which has been observed by some

investigators[4,5,11] may be due to lumps of sludge in the blood which are caught in the small blood vessels and might interfere with or block the blood flow.

3. Laboratory examinations made concomitantly with the observations on sludge reveal the following: increase in leukocytes in five cases, increase in sedimentation rates in nine cases, and high cholesterol levels in four cases. These changes, however, were mostly temporary in character. Fatty acid determinations, glucose tolerance tests, and prothrombin levels did not disclose significant or lasting abnormal changes. However, in view of the fact that some of the patients did show leukocytosis, higher cholesterol levels, and higher sedimentation rates, it is evident that further studies are indicated.

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Role of Pallidum in Genesis of Some Choreic Movements

E. A. Spiegel, M.D. and H. T. Wycis, M.D.

THE role of the pallidum in the mechanism of choreic and athetotic movements has become a highly controversial subject. While one group of authors[1,2] place the neural mechanism producing these involuntary movements chiefly in the globus pallidus (pallidal theory), others are guided by the experience that the ablation of parts of the precentral gyrus may abolish these movements (cortical theory), thus questioning the importance of the basal ganglia in this mechanism.[3,4] The discovery that stimulation of certain cortical areas, particularly of the so-called strip area 4s, may inhibit not only the contraction of contralateral skeletal muscles[5] but also the electrical activity of area 4, and that this latter inhibition takes place by way of a system in which the striatum is intercalated,[6] induced Bucy[4] to assume that these involuntary movements are caused by interference with impulses that originate in the suppressor strip. This author outlines an inhibitory circuit originating in 4s and passing through the caudate nucleus, globus pallidus, ventrolateral nucleus of the thalamus, and from there to the precentral gyrus, particularly areas 6 and 4. According to this theory, the globus pallidus is part of the suppressor circuit that inhibits the electrical activity of areas 4 and 6 as well as the impulses for hyperkinesis in chorea and athetosis that are supposed to originate in these areas.

Thus there are two contrary views, one holding that the neural mechanism of involuntary movements in chorea and athetosis originates in the globus pallidus, the other that cortical impulses innervating such movements are suppressed by way of the pallidum. Isolated observations in cases of athetosis with an incomplete pallidal lesion[7] are hardly sufficient to support this latter theory. In the overwhelming majority of cases, in which definite extensive bilateral lesions in the pallidum were observed, as for instance in carbon monoxide poisoning, hypokinesis rather than hyperkinesis resulted from such lesions. Furthermore, in the experiments reported by Dusser de Barenne, Garol and McCulloch[6] a large lesion in the globus pallidus did not prevent the suppression of electrical activity in the cortex on strychninization of 4s, so that the pallidum does not form a necessary part of the suppressor pathway arising in 4s. Recently Sloan and Jasper[8] have shown that suppression

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of cortical electrical activity ascribed only to certain "suppressor areas" is actually due to the spreading depression of Leao[9] so that the existence of these "suppressor areas" has become rather questionable. Despite these difficulties, Bucy's theory has been widely accepted.

Experiences in four cases of Huntington's chorea, in which circumscribed electrolytic lesions were produced in the globus pallidus bilaterally by means of the stereotaxic method, should be of interest. One of these cases was complicated by the appearance of a hemiplegia contralateral to the pallidotomy, caused either by the encroachment of the lesion upon or interference of blood supply to the internal capsule. This case of course does not permit any conclusions regarding the role of the pallidum in the genesis of involuntary movements. It emphasizes the desirability of placing lesions of the pallidum in its lateral part in order to avoid impairment of the internal capsule as much as possible. In another case a decrease of the involuntary movements was obtained on one side only despite bilateral pallidal lesions. In two patients the pallidal lesions resulted in definite diminution or nearly complete elimination of the involuntary movements after the first operation (right pallidotomy) on the left side, and after a second stage (left pallidotomy) also on the right side.

The effect of these lesions was recorded by motion pictures as well as electromyograms. While the first method permits one to visualize the involuntary movements and their changes in toto, electromyographic tracings seem to be more suitable for a comparison of these movements before and after the operative procedure. Figures 1 to 3 are from one of the two last mentioned cases, a 60 year old colored man who suffered from bizarre, involuntary, generalized movements as did his three brothers. The electromyograms of the shoulder, forearm and the calf muscles were recorded before and after the electrolytic lesions were placed in the lateral part of the right pallidum (figures 1 and 2), and after an analogous operation of the left pallidum (figure 3). The pallidal lesions were produced by means of three punctures directed obliquely from anterodorsally to posteroventrally intersecting the horizontal line through the pineal center at an angle of 75°. They were made with a stainless steel wire, 0.8 mm. in thickness which was insulated except at the tip, and served as anode of direct current. For each lesion a current of 3 milliamperes was applied for one minute. The following coordinates were used:

*Anterior to pineal center**	*Lateral*	*Relation to horizontal plane through pineal center*
29 mm.	16.5	0, −2
25 mm.	19	+2, 0, −2, −4
21 mm.	20	+2, 0

*Measured in the horizontal plane through the pineal center.
0 means horizontal plane; + = above; − = below this plane.

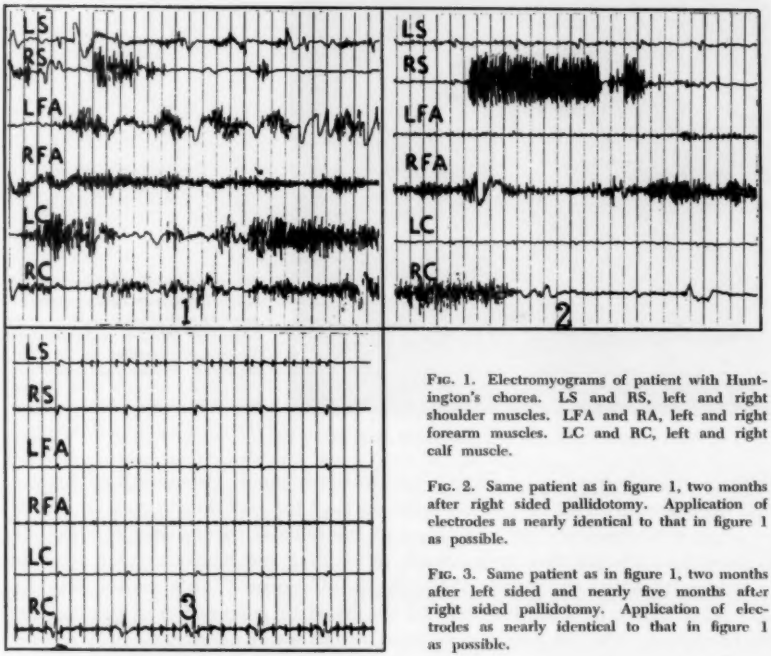

FIG. 1. Electromyograms of patient with Huntington's chorea. LS and RS, left and right shoulder muscles. LFA and RA, left and right forearm muscles. LC and RC, left and right calf muscle.

FIG. 2. Same patient as in figure 1, two months after right sided pallidotomy. Application of electrodes as nearly identical to that in figure 1 as possible.

FIG. 3. Same patient as in figure 1, two months after left sided and nearly five months after right sided pallidotomy. Application of electrodes as nearly identical to that in figure 1 as possible.

After the first right-sided operation a droplet of Pantopaque was injected corresponding to the highest lesion along the middle puncture line (25 mm. anterior to the pineal center). A roentgenogram taken before the second left-sided operation is reproduced in figure 4. In this roentgenogram the location and direction of the three punctures planned in the left pallidum at the same distances from the pineal gland as in the preceding right-sided operation are marked. The figure shows that the Pantopaque droplet instilled at the first operation lies along the course of the central of the three lines a few millimeters above the horizontal line through the pineal center.

The electromyograms show that after the right-sided operation practically no involuntary movements were recorded from the above-mentioned muscle groups on the left side, and after the additional right-sided pallidotomy only slight twitchings appeared in the calf muscles on the right side. The only involuntary movements noticeable two years after the second operation were slight twitchings of the forehead muscles on the left side, while on the right side, slight jerking of the shoulder, extensor-flexor movements of the thumb, and extension of the toes were noted. Signs of a lesion of the left internal capsule subsided within a few weeks. The only residue of a lesion of the pyramidal tract on the right side was a slight weakness of the left lower limb. Muscular

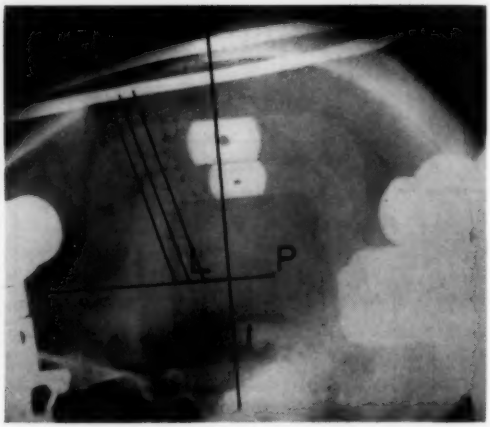

FIG. 4. Lateral roentgenogram of the patient whose electromyograms are shown in figures 1 to 3. I = interaural line; L = Pantopaque droplet corresponding to the middle lesion in the right pallidum; P = pineal body. The three oblique lines indicate the punctures.

rigidity did not develop, probably because only small circumscribed lesions had been produced and relatively large parts of the pallidum remained intact.

Thus our experience seems to support the pallidal theory, which considers Huntington's chorea due to a release of pallidal mechanisms. Our work is in agreement with experiments of Mettler and Carpenter[10] in primates showing that subthalamic hyperkinesis may be abolished by fulguration of the lenticular fasciculus. The inhibitory apparatus where lesion induces such a release has been located in the striatum, since pathologic changes, chiefly degeneration of the small cells of this ganglion, have been found in Huntington's chorea.[1,11–13]

The experience that ablation of the precentral area may relieve hyperkinesis has been quoted as an argument against such a view.[3] However, it would seem that this experience may be integrated into a pallidal theory of the choreic hyperkinesis without much difficulty. It is known that the pyramidal tract does not conduct the efferent impulses innervating these types of hyperkinesis, since such involuntary movements may also occur in cases with severe injury to the pyramidal tract.[14,15] Bucy also assumes that these involuntary movements are due to impulses conducted by a parapyramidal system arising in areas 4 and 6.[4] The fibers innervating the hyperkinesis may travel to the substantia nigra, reticular formation, and basal ganglia. It seems that this latter component merits special consideration. While direct frontopallidal fibers are controversial,[16] there exist numerous observations of frontothalamic fibers originating chiefly in area 6 and ending in various thalamic nuclei, such as the reticular nucleus, the medial nucleus, the anterior portion of the ventral part of the lateral group of the thalamic nuclei.[17] From the thalamus there are definite fiber connections to the globus pallidus (according to Papez,[18] particularly from the medial nuclei). If one assumes that this fronto-thalamo-

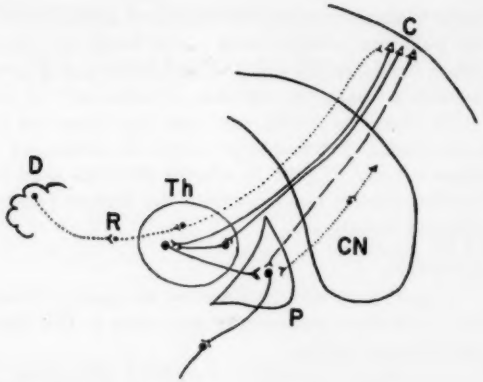

FIG. 5. C = cerebral cortex. CN = caudate nucleus. D = dentate nucleus. P = globus pallidus. R = nucleus ruber. Th = thalamus. ..... = inhibitory pathway. – – – – – = uncertain pathway.

pallidal system (figure 5) activates the associated and other automatic movements localized by Hunt[19] and the Vogts[1] in the pallidum, the pallidal theory of hyperkinesis is compatible with the experience that ablation of the precentral region may favorably influence this type of hyperkinesis. If the impulses conducted by way of the fronto-thalamo-pallidal system find the pallidum in a state of overexcitability due to release from striatal inhibition, then the activating influence of the fronto-thalamo-pallidal system may easily induce a pathologic hyperkinesis.

This discussion has been limited so far to the neural mechanism of Huntington's chorea. The question arises whether the concept outlined above may be applied to other types of chorea. It may be pointed out that areas 4 and 6 receive impulses from the system dentate nucleus–nucleus ruber–lateroventral nucleus of the thalamus. The experience that choreic movements may result from lesions of the superior peduncle[20] suggests that this cerebellofugal system carries inhibitory impuses to areas 4 and 6. If these areas are released from the cerebellar inhibition by lesions in any part of the system, their facilitating or activating influence upon the pallidum becomes pathologically increased and choreic movements may result. Thus choreic movements due to a lesion of the dentatus-ruber system and the possibilities of their treatment by neurosurgical procedures may be explained by the scheme represented in figure 5. According to this concept, impulses arising in extrapyramidal frontal areas and conducted directly or by way of the thalamus to the pallidum are able to activate the mechanisms localized in this ganglion and to produce associated movements, and perhaps also other types of automatic (reactive, expressional) movements. This mechanism will result in pathologic hyperkinesis if either the striatal inhibitory apparatus or the inhibitory dentato-rubro-thalamo-cortical system is injured. Pathologic hyperkinesis may be diminished if the activating impulses from the frontal areas particularly from area 6 are abolished by an operative procedure, sometimes also by lesions of

those thalamic nuclei which transmit cortical as well as emotional impulses to the pallidum (thalamotomy), and finally by circumscribed lesions in the pallidum itself (pallidotomy). The latter procedure as a rule avoids the serious by-effects (paralysis, aphasia, convulsions) of the cortical operations.

It should be emphasized that this discussion has been limited to Huntington's chorea and that type caused by lesions of cerebellofugal fibers. Other types of chorea such as chorea electrica may have a different mechanism. Further studies may elucidate the factors responsible for the production of athetoid movements.

SUMMARY

Experiences with pallidotomy in cases of Huntington's chorea suggest that the involuntary movements appearing in this disease are due to a release of pallidal mechanisms.

A working hypothesis is outlined attempting to explain the neural mechanism in various types of chorea and the effect of operative procedures.

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The Central Nervous System in Thrombotic Thrombocytopenic Purpura

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THE syndrome of thrombotic thrombocytopenic purpura has appeared in the literature under various titles since its original description by Moschowitz[1] in 1925. He reported a case of progressive, severe, febrile anemia in a 16 year old white girl. The pathologic lesions seen at the time of death were described by him as being multiple hyaline thrombi which were widely disseminated and located in the terminal arterioles and capillaries.

Baer, Klemperer and Schifrin[2] reported four cases in 1936 and established the syndrome as a clinical as well as a pathologic entity. To date a total of 30 cases have been described in the American literature and two cases have been recorded by Wallace[3] in the Australian literature. The first eight cases reported[1–6] were females; however, of the 32 cases now recorded, 13 were males. Seven were negroes. The ages of the patients have varied from nine to 66 years.

The central nervous system has been implicated in all of the published cases, and the neurologic symptoms and findings in these cases are recorded in table 1. The following case demonstrates the involvement of the central nervous system.

CASE REPORT

A 33 year old white male was admitted to the U. S. Naval Hospital, Great Lakes, Illinois, on April 2, 1951 complaining of bloody stools and vomiting of blood during the three days prior to admission. Further questioning revealed that he had had a slight cold and a sore throat for at least one day prior to onset of symptoms. The amount of blood in the stool and the vomitus was described as being rather small. There had been some bleeding from the gums and on the day of admission he had noted little red spots scattered over his body. There was no history of previous episodes and the past history was essentially negative. The patient was unable to give any evidence concerning the ingestion of, or exposure to, toxic drugs or chemicals. No history of allergy was elicited.

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The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Navy Department.

Physical examination at the time of admission revealed a pale, icteric, somewhat obese white male who appeared acutely ill. Temperature was 100.0°F. and pulse was 96. He was somewhat apprehensive but rational and cooperative. Numerous petechiae were noted in the palpebral conjunctivae and in the skin of the abdomen and extremities. There were many small hemorrhages in the oral and pharyngeal mucosa. The heart and lungs were negative to percussion and auscultation. Blood pressure was 154/80 mm. Hg. The abdomen was slightly distended and some tenderness was noted in the right upper quadrant. No masses or organs were palpable. Findings on neurologic examination were within normal limits.

Laboratory findings: The urine showed a specific gravity of 1.013, a 2+ albumiuria, a negative sugar, acetone and bile (Harrison) and an occasional leukocyte and erythrocyte per H.P.F. The hemoglobin was 12.5 Gm. per 100 ml.; erythrocytes, 4,100,000 per cu. mm.; leukocytes, 9,450 per cu. mm.; hematocrit, 29. The differential count revealed 64 per cent segmented neutrophiles, 5 per cent unsegmented neutrophiles, 21 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. Platelet count was 220,000 per cu. mm.; nonprotein nitrogen 81.5 mg. per 100 ml.; total protein 5.41 grams; albumin 4.09 grams; and globulin 1.32 grams. Bleeding time 3 minutes 45 seconds. Coagulation time 6 minutes 15 seconds.

The patient remained in the hospital for a period of six days expiring early on the morning of the sixth day. For the first three days the temperature ranged from 99° to 101° F. Respirations were 20 to 24 per minute and pulse was between 76 and 100 per minute. On the fourth hospital day a gradual rise in temperature, pulse and respirations was noted and just before death the temperature was 106° F., pulse 116, respirations 45.

The patient was given repeated transfusions of whole blood which did not prevent a progressive fall in red count and hemoglobin. On the second hospital day there was increased bleeding from the gums. The patient complained of severe low back pain which could only be relieved with opiates. This complaint persisted until he lapsed into coma.

On April 5 (the third hospital day) the Rumpell-Leed (cuff) test was positive. Urine specific gravity was 1.014; 1+ albuminuria; 25 to 30 erythrocytes per H.P.F. Hemoglobin was 8 Gm. per 100 ml.; erythrocytes 2,820,000 per cu. mm.; hematocrit 26. Differential count: 67 per cent segmented neutrophils, 6 per cent unsegmented neutrophils, 17 per cent lymphocytes, 6 per cent monocytes, 4 per cent eosinophils, and 2 per cent basophils. Platelet count was 136,000 per cu. mm. Kahn test was negative; blood cultures taken on three successive days showed no growth. Icterus index was 40 units. Prothrombin time was 15 sec. (control 14 sec.). There was inadequate clot retraction at the end of 24 hours. Sternal bone marrow smears revealed a cellular marrow which was hyperplastic with maturing megakaryocytes. There was no evidence of leukemia.

This same day the patient had a convulsion involving the upper extremities, which lasted for five minutes; following the seizure all deep tendon reflexes were absent. Hoffman and Babinski signs were negative. The patient became very restless and then had several generalized convulsions before he lapsed into coma. He continued in this state until his death on April 7.

In addition to repeated transfusions and opiates the patient had received intravenous fluids, penicillin, Aureomycin, vitamin C and vitamin K during his hospital course. Urinary output had remained good, being 300 cc. in the final 24 hours.

*Gross pathologic observations:** Gross examination disclosed a mild icterus. Numerous petechial hemorrhages were seen scattered in the skin of the shoulders and upper thorax anteriorly with small numbers elsewhere over the body. On the right lateral border of the tongue there was a small hematoma measuring 1 cm. in diameter. Clotted blood was found in the mouth.

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*I wish to thank R. H. Fuller, Commander, MC, USN, for his description of the pathologic findings in this case.

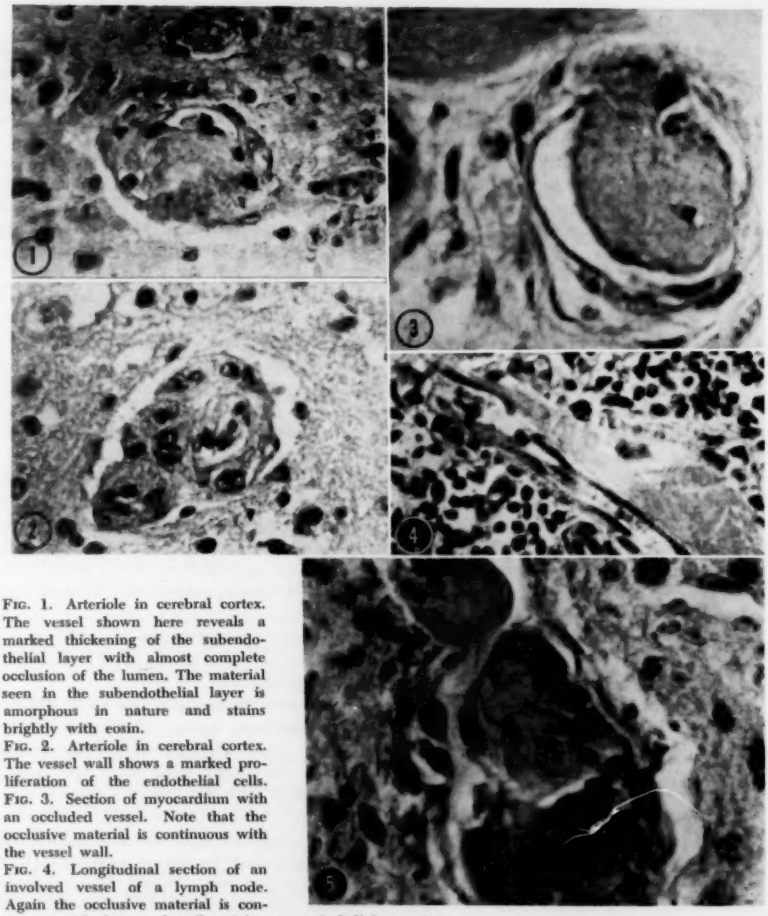

FIG. 1. Arteriole in cerebral cortex. The vessel shown here reveals a marked thickening of the subendothelial layer with almost complete occlusion of the lumen. The material seen in the subendothelial layer is amorphous in nature and stains brightly with eosin.

FIG. 2. Arteriole in cerebral cortex. The vessel wall shows a marked proliferation of the endothelial cells.

FIG. 3. Section of myocardium with an occluded vessel. Note that the occlusive material is continuous with the vessel wall.

FIG. 4. Longitudinal section of an involved vessel of a lymph node. Again the occlusive material is continuous with the vessel wall and has an endothelial covering.

FIG. 5. Cerebral vessels showing complete occlusion of the vessel lumina by the amorphous thrombotic material.

The scalp contained numerous small petechial hemorrhages in the galea. Reflection of the dura revealed a somewhat edematous, pale brain. The spinal fluid was clear. The brain weight was 1500 Gm. Multiple gross frontal sections of the brain and brain stem revealed several small hemorrhages which were perivascular in location. In the cerebrum these were also noted in the midbrain just beneath the inferior colliculi. There was some swelling of the cerebral white substance and a moderate cerebellar pressure cone was noted.

Five hundred ml. of straw-colored fluid was found in the right pleural cavity. The left lung weighed 650 Gm. and the right lung 750 Gm.; there was considerable congestion and

edema of these organs. A caseous and partially calcified Gohn complex was found in the left lung.

The pericardial cavity was distended by 500 ml. of fluid which had a straw-colored appearance and was slightly cloudy. The pericardial surfaces, particularly the epicardium, contained several hemorrhagic areas. These extended from the epicardium along the great vessels to the parietal pericardium. In the myocardium there were large hemorrhagic zones, although the normal firmness was retained.

The stomach and duodenum showed congestion of the mucosa but no large amount of hemorrhage. A tiny healed ulcer was found in the first portion of the duodenum.

The spleen was enlarged, weighing 650 Gm. The capsule was thin, transparent and tense. The cut surface of the spleen revealed normal parenchymal markings with a dark cyanotic color to the red pulp. The adrenals were not enlarged. Numerous small hemorrhages were seen in the adrenal cortices.

The left kidney weighed 260 Gm. and the right kidney 250 Gm. The capsules stripped easily. Petechial hemorrhages were visible in the capsule and pelvic mucosa. The urinary bladder was contracted. Its mucosa was edematous and large hemorrhagic zones were seen in the fundus.

Microscopic observations: The significant microscopic finding was widespread occlusion of arterioles and capillaries. These lesions were frequent in all organs except the lungs and liver. In the latter organ a few were noted in the capsule and periportal spaces but none in the hepatic sinusoids.

The occlusive material stained brightly with eosin. It was amorphous in nature and appeared somewhat granular. This caused some distention of the affected vessels. The thrombus was covered with endothelial cells. In many sections there was similar amorphous material seen in the subendothelial layer of the vessel wall; this was found in many vessels without the presence of a thrombus. Proliferation of the endothelium of the vessel wall was seen in several areas. In the areas of the involved vessels, perivascular hemorrhages were seen.

Sections of the kidneys revealed an eosinophilic protein precipitate in the subcapsular spaces. The convoluted tubules were somewhat distended and several contained eosinophilic protein casts. There was moderate acute proliferative glomerulitis.

Sections of the brain fixed in formalin and stained with hematoxylin and eosin showed changes in the blood vessels which were similar to those seen throughout the rest of the body. The meningeal vessels appeared normal. The vessel changes were concentrated mainly in the gray matter and were widely scattered. In several areas there were small hemorrhages around the affected vessels. Also associated with the vascular lesions were minute foci of hemorrhagic or ischemic necrossis.

The usual vascular lesion involved the precapillary arteriole and was first manifested by thickening of the vessel wall. This thickening appeared to be due to swelling of the endothelial cells, the reticular fibers and the adventitial pericytes. Mitotic figures among these enlarged endothelial cells were seen frequently. The swelling and proliferation of endothelial cells in some areas occluded the lumen of the vessel without the formation of a thrombus. In the brain these prethrombotic vascular changes were more numerous than those associated with thrombi. With thickening of the vessel walls the vascular bed in the affected areas was very prominent as observed under the lower magnification. The next stage in the evolution of the vascular lesion appeared to be the deposition of an amorphous material in the thickened vessel wall. The amorphous material stained brightly with eosin and was associated with fibrinoid necrosis of the vessel wall. In many areas a granular eosinophilic thrombus was found at this site and was occasionally covered by a layer of proliferating endothelial cells. The affected vessels were distended beyond their normal caliber.

The posterior pituitary lobe and the pituitary stalk contained many of these vascular occlusive lesions, but none were seen in the anterior lobe.

DISCUSSION

It has been pointed out by Singer, Motulsky and Shanberge[16] that this syndrome and its clinical manifestations are the result of three distinct phenomena which are not seen together in any other clinical entity. They are: 1. hemolytic anemia, 2. thrombocytopenic purpura, 3. findings due to occlusion of small arterioles. The third part of the triad is usually manifested clinically by signs and symptoms of altered central nervous system activity.

The onset of illness frequently follows a mild upper respiratory infection in a previously healthy individual. Several authors have reported the onset of acute illness following a period of vague ill health.[2,10,15] The syndrome has also been described in patients who have been ill with some chronic disease such as tuberculous enteritis,[15] glomerulonephritis,[13,15] and arthritis.[18] The initial complaints may be insidious in onset, vague and non-localizing. These include fever, headache, weakness, nausea, vomiting, arthralgia, myalgia and anorexia. Pallor, icterus, petechiae, epistaxis, hematuria and hematemesis follow. Symptoms of altered central nervous system activity appear at this stage; these are chiefly cerebral in nature and include dizziness, delirium, confusion and lethargy progressing to coma. A change in the state of consciousness usually occurs a few hours prior to death. Other neurologic disturbances may include aphasia, apraxia, facial paralysis and weakness or paralysis of one or more extremities.

The usual duration of the illness has been recorded from four days in a case reported by Gore[15] to three months. Mecham, Orbinson, Heinle, Steele and Schaefer[19] have described a very unusual case with three year survival. This case had been treated with splenectomy and ACTH. The typical lesions of the syndrome were found in the patient's spleen which was removed three years prior to the time of death. Splenectomy has been performed in four other cases,[2,9,12,13] and in each instance death occurred shortly after the operation and before any therapeutic effect could be evaluated.

Laboratory findings show the manifestations of a hemolytic anemia, with the erythrocyte count falling to two million or less per cu. mm. The anemia is normocytic and normochromic. Reticulocytes are frequently increased and bone marrow studies reveal hyperactivity of the erythrogenic series. There is an increase of serum bilirubin and fecal urobilinogen.

The leukocyte count is normal or increased with a "shift to the left." There is a decrease in the number of circulating thrombocytes. The bleeding time typically is prolonged with normal clotting time; clot retraction is defective. The tourniquet test is positive.

Singer, Motulsky and Shanberge[16] have pointed out that the features of hemolytic anemia constitute one of the diagnostic criteria of the syndrome. They were unable to demonstrate any existing hemolytic activity in the plasma; however, in one case there was found an increased mechanical fragility of the erythrocytes of thrombotic thrombocytopenic purpura. They also noted

TABLE 1

SYMPTOMS AND FINDINGS IN 30 CASES OF THROMBOCYTIC THROMBOCYTOPENIC PURPURA PREVIOUSLY REPORTED IN THE AMERICAN LITERATURE

Case	*Sex Color*	*Age*	*General Clinical Findings and Symptoms*	*Neurologic Findings and Symptoms*	*Duration of Illness*
Moschcowitz[1]	F, W	16	Weakness, joint pains, pallor, fever, petechiae and (?) jaundice	Left hemiparesis, Kernig sign and coma	14 days
Baehr, Klemperer, Schifrin[2]	F, W	9	Listlessness, hematuria, pallor, petechiae and splenomegaly	Retinal hemorrhages	7 weeks
Baehr, Klemperer, Schifrin[2]	F, W	18	Weakness, pallor, icterus and petechiae	Headache and convulsions	2 months
Baehr, Klemperer, Schifrin[2]	F, W	22	Urticaria, purpura, nausea and vomiting	Delirium, stupor and retinal hemorrhages	9 days
Baehr, Klemperer, Schifrin[2]	F, W	48	Upper respiratory infection, purpura and icterus	Right hemiparesis, retinal hemorrhages and coma	2 weeks
Gitlow and Goldmark[4]	F, W	18	Upper respiratory infection, purpura, enlargement of spleen and liver, and generalized aches	Right hemiparesis, coma, and retinal hemorrhages	18 days
Altschule[5]	F, W	50	General malaise, abdominal pain, generalized aches, hematemesis and epistaxis	Headaches, dizziness and confusion. Left facial weakness which was transient and disappeared after a few minutes	10 days
Bernheim[8]	F, W	33	Weakness, dermatitis, pallor, purpura and anorexia	Left facial weakness, hemianesthesia, convulsions, headache and coma	2 weeks
Trobaugh, Markowitz, Davidson and Crowley[7]	M, W	24	Upper respiratory infection, icterus, purpura, vomiting and abdominal pain	Restlessness, stupor, coma and convulsions	15 days
Carter[8]	M, N	66	None	Confusion, aphasia, unequal tendon reflexes, right Babinski and coma	12 days
Engel, Schemker, Humphrey[9]	F, N	15	Sore throat, fever, malaise, purpura, hematuria, menorrhagia, vomiting and ECG changes. 5 weeks later: recurrence of systemic and hemorrhagic symptoms	Blurred vision, headache and delirium	30 days
				Coma, deviation of head and eyes to right, left hemiparesis and right facial weakness	7 days
Fitzgerald, Auerbach, Frame[10]	M, W	34	Nausea, vomiting, abdominal pain, pallor and purpura	Restlessness, confusion and coma	3 weeks
Fitzgerald, Auerbach, Frame[10]	F, N	27	Urticaria, faintness, epistaxis, hematemesis, menorrhagia and pallor	Stupor progressing to coma	1 week
Fitzgerald, Auerbach, Frame[10]	M, W	24	Rheumatic fever, precordial pain, syncope, joint pains, chills, fever, epistaxis, hematemesis, hematuria, pallor and purpura	Status epilepticus, confusion and coma	1 month
Singer, Bornstein and Wile[11]	F, W	11	Weakness, fever, upper respiratory infection, anorexia and nausea	Confusion, dizziness, paresthesia of extremities (disappeared in two hours) and coma	20 days

TABLE 1—*(Continued)*

Case	*Sex Color*	*Age*	*General Clinical Findings and Symptoms*	*Neurologic Findings and Symptoms*	*Duration of Illness*
Green, Rosenthal[12]	M, W	69	Nausea and anorexia	Dizziness, headaches, aphasia, and confusion which were intermittent. Weakness of right upper extremities with increased biceps reflex	3 weeks
Green, Rosenthal[12]	F, W	33	Palpitation and generalized weakness	Tinnitus, headaches, aphasia, transient confusion, stiff neck, retinal hemorrhages, right facial weakness, right hemiplegia	21 days
Muirhead, Grass, Hill[13]	F, W	14	Jaundice, dyspnea, abdominal pain, nausea, vomiting and bloody stools	Transient paralysis of the left arm and mental deterioration terminally	22 days
Erlich, Seifter[14]	F, N	24	Abdominal pain, hematemesis, epistaxis and hematuria	None recorded	5 days
Gore[15]	F, W	25	Fatigue, pallor and weakness	Headache, delirium, convulsions and coma	14 days
Gore[15]	M, N	23	Night sweats, cough and fever	Spasticity, convulsions and coma	30 days
Gore[15]	M, W	21	Weakness, pallor and malaise	Coma	4 days
Gore[15]	M, W	44	Abdominal pain	Headache, dizziness, deafness, aphasia, convulsions and coma	13 days
Gore[15]	M, N	53	Dyspnea, substernal pain, and urinary frequency	Sudden confusion and weakness of right extremities	4 days
Singer, Motulsky, Shanberge[16]	F, W	23	Weakness, petechiae, hematuria, lumbar pain, nausea and vomiting	Headache, confusion, right hemiparesis, right facial weakness and motor aphasia. Hemiparesis and aphasia disappeared after five days. Left external rectus paresis and coma	9 weeks
Wyatt, Lee[17]	M, W	53	None	Bilateral papilledema, vertigo and mental confusion	7 days
Beigelman[18]	F, W	43	Swelling of fingers and legs, precordial pain, palpitation, malaise, dyspnea, nausea and vomiting	Headache and dizziness	3 months
Beigelman[18]	M, W	60	Chills, fever and lumbar pain	None recorded	2 years
Meacham, Orbison, Heinle, Steele and Schaefer[19]	F, N	54	Weakness, nausea and vomiting	Dizziness, aphasia, confusion and right-sided convulsions. Aphasia cleared temporarily before death	38 days
Meacham, Orbison, Heinle, Steele and Schaefer[19]	F, W	43	First admission: Weakness and "chilly sensation."	Lethargy and fainting.	3 years
			Second admission: None	Poor memory, slowness of speech, lethargy, apathy and right hemiparesis. Right pupil was larger than the left	

that the lysolecithin fragility of the cells in thrombotic thrombocytopenic purpura was normal whereas the spherocytes of familial hemolytic jaundice show increased saline and lysolecithin fragility.[16,20] The Coombs' test for the demonstration of the presence of immune bodies which form a globulin coating on the surface of the erythrocytes is negative; this is positive in some acquired hemolytic anemias. It has been reported that the anemia seen in this syndrome is not due to bleeding into the tissues.[11] However, the writer is of the opinion that the anemia could readily be explained on that basis, for it is believed that the red cells lost in these hemorrhages are then hemolyzed and the breakdown products of the hemolyzed cells give the findings of a hemolytic anemia.

Baehr, Klemperer and Schifrin[2] regarded the thrombopenia as developing from the loss of thrombocytes in the blood stream as they form the thrombotic lesions. Others[19] concluded that the thrombopenia is not the result of deposition of large numbers of platelets in the occluded vessels, but may be the result of a process similar to that producing idiopathic thrombocytopenic purpura.

The thrombotic lesions are found in several organs and are located in the arterioles and capillaries. Moschcowitz[1] described these as "hyaline" plugs. Baehr, Klemperer and Schifrin[2] recognized these thrombi as agglutinated blood platelets. The thrombi appear in various parts of the body in a succession of attacks with little or no evidence of tissue necrosis. The staining properties of the hyaline differ from those obtained with erythrocytes, leukocytes, bacteria, fibrin, hemosiderin and hemoglobin.[16] However, Weiner[21] considers that the thrombi are composed of "partially lysed autoconglutinated red cells," despite the negative Coombs' test. Few thrombi are found in the lung capillaries and liver sinusoids, areas which would readily be involved if the lesions were secondary to spontaneous agglutination of the blood. Gore[15] demonstrated that both platelets and the occlusive material will give positive reactions with the periodic acid-Schiff reagent. This reaction is also positive in many types of tissue involving degenerative changes in vessels and thus cannot be considered specific.[19]

Careful pathologic search by Gore[15] revealed focal lesions within the walls of the arterioles and capillaries upon which the platelet thrombi formed and grew along the length of the vessel wall. He termed these "prethrombotic lesions," consisting of an accumulation of hyaline material which is subendothelial in location. The hyaline material grows in size until it ruptures the overlying endothelium; platelets accumulate to cover the defect and in doing so occlude the involved vessels. A longitudinal demonstration of the prethrombotic lesion is shown in figure 4.

Meacham, Orbison, Heinle, Steele and Schaefer[19] have described multiple aneurysms of the arterioles and precapillaries containing thrombi. The development of these vessel dilations may be explained by the presence of defective walls and/or the increased intravascular pressure behind the thrombus.

Petechial hemorrhages which are readily visible to the naked eye are found near the thrombosed vessels. Parenchymal damage of the involved tissues is

only slight. Neurons seldom undergo complete degeneration but they may show tinctorial changes. Adams, Cammermeyer and Fitzgerald[22] were unable to demonstrate any massive destruction of myelin or axis cylinders near the altered blood vessels.

The transient characteristics of the neurologic symptoms may be explained by the persistence of some patent vessels, for rarely are all vessels to an area involved. The neurologic findings are indicative of focal or diffuse cerebral involvement. A subdural hematoma was reported in one case.[11] Subarachnoid bleeding has been reported in several cases. Examination of the spinal fluid may reveal normal or bloody fluid which is under normal or increased tension.

The etiology of this syndrome is unknown. However, Schwartzman, Klemperer and Gerber[23] were able to produce lesions similar to those found in "generalized platelet thrombosis" by inducing the Schwartzman phenomenon experimentally in animals. Hypersensitivity to the sulfonamides was demonstrated in two cases of thrombotic thrombocytopenic purpura.[9,10] Erlich and Seifter[14] are of the opinion that iodine was the etiologic factor in their case. They considered the iodine as causing an antigen-antibody reaction. The antibodies thus produced caused agglutination or disintegration of the iodine-laden thrombocytes which in turn produce the capillary thrombi.

The relationships of this syndrome to the collagen diseases has been discussed by several authors. Fitzgerald, Auerbach and Frame[10] considered that there was no relationship. Contrary to this, Beigelman[18] has postulated that in the collagen diseases the location of the hypergic reaction is all important. He adds that this reaction is located in the intima in thrombotic thrombocytopenic purpura, within the walls of the vessels in periarteritis nodosa, and in the perivascular mesenchyme in lupus erythematosus. Brothers of patients have died with periarteritis nodosa,[2,6] and a sister of one of the patients had lesions typical of lupus erythematosus at the time of death.[11] A recently reported case revealed lesions of polyarteritis nodosa and thrombotic thrombocytopenic purpura.[24] It is believed that the resemblance of this syndrome to the collagen diseases should be considered by future investigators.

Therapy has been limited and totally unsuccessful in the fulminating cases. The progressive anemia is unaffected by repeated transfusions. Splenectomy has been performed in several cases with no alteration in the course of the disease; however, one case[16] survived one attack during which a splenectomy was performed, the second and fatal attack occurring in this case three years later. More adequate evaluation of this procedure is necessary since many of the cases were moribund at the time of surgery. ACTH has been used in but one case[16] so its therapeutic value cannot be assessed at this time.

SUMMARY

A case of thrombotic thrombocytopenic purpura is summarized.

The pathology of the syndrome and its relationship to the collagen diseases are discussed.

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Loss of consciousness is invariable in all severe epileptic fits. It is only in minor seizures that, in rare cases, some consciousness may be retained. In many instances the loss of consciousness occurs at the very onset of the fit, before or at the same time as, the earliest convulsive symptom, so that the patient knows nothing of the onset. In other cases, as already detailed, consciousness may be retained until after some other symptom has occurred, of which the patient is conscious, as the warning of the fit, and, in the description of these warnings, full information as to the period at which loss of consciousness occurs has already been given.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Cerebral Complications of Serum Sickness

A. M. Park, M.D. and J. C. Richardson, M.D.

SERUM sickness became a recognized disease with the introduction of diphtheria antitoxin in 1895. With the development and more prevalent use of other therapeutic antisera of animal derivation, it has been a frequent complication of both active and preventive treatment of many diseases. It is one of the more common manifestations of hypersensitivity and is closely related to true anaphylaxis (a rarity in humans) and other allergic disorders.

Rich[1] divides hypersensitivity into two types, the first as exemplified by the tuberculin type of reaction, and the second by the anaphylactic type, as exemplified by serum sickness. The term "serum sickness" has been used by some to include various drug sensitivities, but in this presentation it will be limited to the reaction of the body to an injected foreign protein.

The frequency of serum reactions is indicated in a review of patients treated with rabbit sera for pneumococcal pneumonia in the days preceding chemotherapy and antibiotics. In this review of 2,340 patients, Rutstein et al.[2] found that 31 per cent had some reaction related to the serum itself. The incidence of reactions was definitely higher (45 per cent) in those patients with a history of asthma or other allergic states. Eason and Carpenter,[3] in treating a group of 49 patients with anti-scarlet fever serum for acute rheumatic polyarthritis, found that a reaction to the serum itself was evoked in 75 per cent. Horse serum is said to be more productive of serum sickness than rabbit serum.

The morbidity, therefore, is relatively high following serum therapy, but actual mortality would appear to be very low. In a series of 350,000 children treated with diphtheria antitoxin reported by Park[4] in 1913 there were only five deaths attributable to the serum itself. Longcope[4] in 1941 stated that, as far as he knew, no deaths had occurred in adults from serum administration.

The usual manifestations of serum sickness are well known and consist of fever, urticaria, joint pains with or without effusion, headache and general malaise. There is frequently a generalized lymphadenopathy with leucocytosis, and albuminuria with casts. The symptoms come on within four to ten days of the administration of the serum and may last for several days, even a week, before gradually subsiding. Besides these more generalized manifestations,

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symptoms and signs have been described in relation to the heart, other internal organs, particularly lung and kidney, and to the nervous system. We shall consider the nervous system complications in more detail, with particular reference to the cerebral manifestations thereof.

INVOLVEMENT OF THE PERIPHERAL NERVOUS SYSTEM

The first recorded instance of involvement of the nervous system in serum sickness was by Gardere and Gangolphe[5] who in 1908 reported a case of what is now termed "serum neuritis." Since then, reports of nervous system damage in serum disease have increased in number. In 1936 Paillos[6] gave an extensive account of serum sickness as it pertained to the nervous system, with an excellent review of the literature.

Generally speaking, involvement of the nervous system is of two main types, peripheral and central. The entity referred to as serum neuritis is the most common example of peripheral type of damage.

Serum neuritis in its most typical form consists of a unilateral brachial neuritis with particular involvement of the fifth and sixth cervical roots. It consists of motor weakness with subsequent wasting, sensory changes including considerable pain and burning, with reflex changes of the appropriate distribution. Recovery, although usually complete, may take many months. The disturbance makes its appearance with the more generalized manifestations of serum sickness and progresses rapidly.

Other localized varieties of radiculoneuritis and neuritis have been observed, with lesions referable to various peripheral nerves and trunks, such as the median, ulnar and sciatic nerves.

Isolated lesions of the cranial nerves have also been described. Roger and Paillos[7] cite rare instances of palatal and pharyngeal paralysis, facial palsy, oculomotor palsy and involvement of the recurrent laryngeal nerve. Involvement of the labyrinth has given rise to vertiginous attacks, and deafness has also been reported. Optic neuritis may also be observed.

In addition to more localized damage to peripheral nerves, a more generalized polyneuritis which resembles that of acute infectious polyneuritis or the Guillain-Barré syndrome, and even an acute ascending paralysis of the Landry type, may be a picture seen with serum sickness.

Bennett,[8] reviewing the literature in 1939, was able to find 115 cases, mainly those of the brachial variety, and added five more to the list. The bulk of the case reports were from France, (70), but 29 were found in the English literature and others in smaller numbers elsewhere. Hughes[9] added six more cases in 1944. These reviewers noted occasional instances of cerebral damage in serum sickness, but did not elaborate on them.

INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

Spinal Cord

In several of the cases of generalized polyneuritis accompanying serum sickness, the presence of pyramidal tract signs with extensor plantar responses

and sensory disturbance corresponding with a spinal level have suggested the presence of some lesion of the spinal cord. No instances are on record, however, of a purely spinal lesion with paraplegic signs.

Cerebral Functions

Diffuse Type. The exact frequency of cerebral injury in serum sickness is difficult to know. Many authors believe that a diffuse type of damage, no matter how mild, is the rule rather than a rarity.

In many cases of serum sickness changes in the cerebrospinal fluid have been demonstrated even in the absence of signs of central nervous system injury. A raised pressure, increase in protein content, increase in cells have been observed in patients who had no other symptoms than headache and drowsiness. Occasionally, however, meningismus, convulsions, diplopia, somnolence and even coma without localizing signs, are indicative of diffuse cerebral damage. This type of lesion has been described as a "neuro-allergic encephalitis" by Windorfer.

The following case report is perhaps illustrative of this type of disturbance. At the height of his illness there was considerable headache and apathy with increased cells in the cerebrospinal fluid and focal disturbance of the brain by electroencephalogram. In the convalescent period the patient developed attacks suggestive of focal epileptic attacks which gradually cleared within six weeks of discharge from hospital.

Case 1. A 19 year old male whose previous health was good. He received a minor burn of the forearm on February 12, 1952, and was given 10 cc. antitetanus serum in four doses because of sensitivity to skin test. Five days later, he developed pains in the axillae, shoulders and neck with general malaise and fever. By the eighth day he had become acutely ill, with severe headache, apathy, pains in most of the joints, swelling of the hands, wrists and elbows, ankles and knees, and he was admitted to hospital. Temperature was 104°. There was marked generalized lymphadenopathy. No urticaria was present but the skin was warm and moist. There was 4 plus glycosuria, with blood glucose of 226 mg. per cent. The white blood count was 14,800. The cerebrospinal fluid was under slightly increased pressure, with 14 lymphocytes per cu. mm., but normal protein. The electroencephalogram showed a rather widespread abnormality, particularly in the right central region.

The patient was treated with oral cortisone, 200 mg. daily, and was afebrile in 24 hours. Three days after admission he was asymptomatic and joint and lymph node swellings disappeared. The blood glucose was normal.

Shortly after discharge he began having attacks lasting 25 seconds in which vision blurred and objects would dance and he would sway. At first he had two to three attacks per day, but after six weeks they had become less frequent and eventually ceased. He was seen in June 1952, and was well, having no complaints.

A mild, transient disturbance of this sort is probably quite common in serum sickness. In some cases, delirium, increased irritability and confusion are prominent features. Roger and Paillos[7] have also reported instances in which patients developed cerebellar signs and even choreiform movements of a transient nature.

Focal Types. The rarest manifestation of nervous system damage in serum sickness is that of focal cerebral injury. The first case was reported by Morichau-Beauchant[10] in 1923. Since then, only eight further cases have been

reported, all but two from the French literature.[7,11-14] Foster Kennedy[15] in 1929 and Edison Fisher[16] in 1949 presented the two cases from the United States.

In the past year, two patients who developed focal brain damage following the injection of serum have come to our attention and are reported here.

Case 2. A 37 year old male had a history of vernal hay fever with occasional asthmatic attacks since the age of 17, with health otherwise good. The patient stepped on nail at work on October 25, 1952. He was given antitetanus serum, 10 cc. in divided doses. Seven days later he became very drowsy, and on the eighth day, awoke with an urticarial eruption over face, arms and trunk. A few hour later he suddenly became unconscious, and was semi-comatose over the next 48 hours. On the eleventh day after injection he regained consciousness, but had a complete right hemiplegia, aphasia, hemiaesthesia and homonymous hemianopsia, which were not influenced by antihistaminic drugs. Six weeks following the injection of the serum he was admitted to hospital for investigation and custodial care. He had regained some power in the right leg, but was still unable to move the right upper limb, and was aphasic with the field defect persisting.

Examination on admission confirmed the right hemiplegia. General physical examination was otherwise not remarkable. Lumbar puncture obtained clear cerebrospinal fluid with no abnormal constituents. Oxygen encephalogram revealed a slight enlargement of the left lateral ventricle. Arteriograms, both carotid and vertebral, showed a normal vascular tree. Electroencephalogram showed a gross dysfunction of the entire left hemisphere.

Several weeks after admission he had a grand mal seizure, beginning focally in the right arm and then becoming generalized. This was controlled by medication. Over the next few months in the hospital he was able to walk with marked hemiplegic gait, but the arm remained powerless, with a gradual increase in tone. He learned a few words but remained aphasic, unable to read, and his comprehension of spoken word was poor. The field defect was still present. He was transferred to a chronic hospital in May 1952.

A very extensive and apparently permanent cerebral injury, with features suggesting a primary vascular lesion, has followed the administration of serum in this case. The findings are compatible with an occlusion of the main trunk of the middle cerebral artery. This vessel, however, filled well in the subsequent arteriograms, and the occlusion was evidently not permanent, although the secondary cerebral damage was irreversible.

Case 3. A 38 year old male was in good health when he received a minor scalp wound November 14, 1951. The wound was sutured, and he was given antitetanus serum, dosage not known. He returned to work and was well for ten days. On November 24, 1951, he developed an itchy rash during the night, involving the trunk and upper limbs. In the morning he was unable to leave his bed because of weakness of the left arm and leg. At first he was completely paralyzed, but later in the day he regained some power in the leg. The next day there was some return of power in the arm.

The patient was examined on November 29, 1951, and was alert but vague and apathetic. There was slight lower left facial weakness, with moderate weakness with increased tone in left extremities. Some apraxia of the left hand was noted. The tendon reflexes were increased on left side, and the left plantar response was extensor in character. Blood pressure was 125/75. The remainder of physical examination was not remarkable.

Two months later he was considerably improved. He complained of weakness on lifting with left hand and dragging of left foot after walking some distance. On examination there was slight spasticity of left arm, with weakness of grip and some loss of dexterity. The left leg was almost normal. The reflex changes persisted.

In this case, the cerebral damage was of a similar nature, but much milder

in its degree, with a reasonably good functional recovery and little residual change.

These cases are comparable in every way to those previously reported in the literature. A table summarizing the recorded cases is presented below.

GENERAL DISCUSSION

Because of the relatively low mortality, there has been little opportunity for adequate study of the pathology of serum sickness, and this is especially true of the nervous system lesions.

Eight patients were studied at postmortem by Rich[17] and two by Clark and Kaplan,[18] but in none of these were there symptoms or signs implicating the nervous system, and the reports are confined to visceral manifestations.

TABLE 1

SUMMARY OF CASES RECORDED IN LITERATURE

Author	*Date*	*Agent (Serum)*	*Latency*	*Manifestation*	*Outcome*
1. Morichau-Beachant (France)	1923	Antitetanus serum	8 days	Complete R. hemiplegia, tachycardia, pulse irregularities, faint heart sounds	Death 4th day, hemiplegia seemed to be improving. Cardiac death?
2. Foster Kennedy (U.S.A.)	1929	Scarlet fever antitoxin	7 days	Partial R. hemiplegia with aphasia, hemianopsia, papilledema	Recovered completely in 5 weeks
3. Charleux, G. (France)	1932	Diphtheria antitoxin	7 days	R. hemiplegia with aphasia. After semicoma	Paresis of arm and leg completely cleared, but aphasia permanent
4. Tzanck et al (France)	1935	Antitetanus serum	8 days	R. hemiplegia including aphasia	Power of limbs recovered quickly, but remained aphasic
5. Roger and Paillos (France)	1936	Scarlet fever antitoxin	10 days (?)	Convulsions, coma, following which L. hemiplegia	Still hemiplegic 2 years later
6. Lemierre et al (France)	1938	Diphtheria antitoxin	7 days	Confusion, stupor with aphasia. (Note—old war head injury with residual R. hemiparesis)	Persisting aphasia
7. Michon and Heully (France)	1946	Antitetanus serum	8 days	Complete L. hemiplegia (B.P. 170/90)	Power began to return in 2 months, but eventual course not known
8. Michon and Heully (France)	1946	Antitetanus serum	8 days	R. hemiplegia, also had brachial neuritis (C5, C6)	Returned to work in 3 months
9. Edison Fisher U.S.A.)	1949	Antitetanus serum	8 days	R. hemiparesis with aphasia	2 wks. began to improve. 5½ months later slight weakness, arm and leg, pause for a word
10. Toronto General Hospital	1951	Antitetanus serum	8 days	Sudden onset of coma, 3½ days. On recovery, complete R. hemiplegia	6 months later, improvement in power of leg, but remains aphasic, right arm powerless
11. Toronto General Hospital	1951	Antitetanus serum	10 days	L. hemiplegia, face, arm and leg	2 months later, slight spasticity and weakness of arm, but little residual disability

Rich feels that the collagen-containing media of the smaller arteries is the main shock-organ of anaphylactic reactions, both experimentally and clinically. It is likely that the cerebral vessels, and those supplying peripheral nerves and roots also take part in the general reaction. Anaphylactic injury to endothelium and media leads to increased permeability and even necrosis of the endothelium. Smooth muscle goes into spasm. Collagen fibers may swell and degenerate, and there may be evidence of alteration in their cement substance. He has produced, by the injection of foreign serum into experimental animals, lesions identical to those of periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and even rheumatoid arthritis. The collagen diseases and serum sickness are concluded to be all manifestations of hypersensitivity, due to many agents, in susceptible human subjects.

While some studies on the visceral lesions of serum sickness are available, there are few on lesions involving the central or peripheral nervous system.

Roger, Poursines and Recordier[19] in 1934 reported a case with pathologic studies. The patient had developed tetanus and was treated by massive doses of anti-tetanic serum over a 12 day period, including one dose of 35 cc. given intrathecally. Eighteen days after cessation of therapy the patient developed a generalized polyneuritis and died some three weeks later. At postmortem examination, there was a moderate internal hydrocephalus but the gross examination was otherwise not remarkable. Microscopically, there was a hemorrhagic meningeal exudate, with dilated pial vessels and interstitial cortical edema, mainly perivascular. In the cord, there were similar diffuse vascular lesions of the meninges, with dilatation of the small arteries and small hemorrhages. There were small areas of necrotic degeneration in these foci. The nerve roots and peripheral nerves showed interstitial changes.

Winkelman and Gotten[20] in 1935 reported a similar case with findings on examination which were mainly referred to the spinal cord. At postmortem examination of this patient, there was a marked meningeal infiltration with proliferation of glia and distension of the anterior horn cells. Perivascular infiltrations were present in the white matter, with many glial foci. Similar patches were found in the brain, with numerous areas of necrosis and accumulations of gitter cells.

These findings in human cases correspond closely with those reported by Garcin and Bertrand[21] following repeated anaphylactic shocks in animals. They serve to explain some of the manifestations of serum disease just discussed.

The inference in those cases of hemiplegia associated with serum sickness, is that there has been damage to a major vessel, with or without more scattered diffuse lesions as already seen. Vascular damage is, according to Rich, the essential lesion in hypersensitivity, and the pathologic studies of nervous system damage to date have not given a clear picture of the lesion which must have been present in those patients with clear cut major focal cerebral damage.

We can only speculate then, that in these cases, major arterial damage took place at the height of the reaction, with edema and other changes in the

arterial wall, with permanent parenchymal changes in the substance of the brain secondary to its disturbed blood supply. The arterial changes are undoubtedly capable of complete reversal, but damage to the parenchyma may be lasting.

We have been interested in reporting these cases of allergic encephalopathy and reviewing the nervous complications of serum sickness because of the possible wider implications as well as pointing out the occasional serious reactions to serum injections. Encephalitis, myelitis, polyneuritis and focal neuritis seem to occur in a similar clinical pattern with acute virus exanthemata, infectious mononucleosis,[22] and collagen diseases. As suggested in the studies of Rich, there is some support for an allergic process in periarteritis nodosa and disseminated lupus erythematosus. As suggested by Miller,[23] the postinfective encephalomyelitis of exanthemata such as measles may be a manifestation of hypersensitivity to an antigen. Stillman and Ganong[24] have further expressed a belief in an allergic basis of Guillain-Barré syndrome.

SUMMARY

A brief review of the types of nervous system involvement in serum sickness is presented, with particular reference to focal cerebral lesions.

Two cases of hemiplegia following serum injections are reported and added to the previous nine cases in the literature.

A discussion of the pathology of serum sickness was undertaken with some speculation as to the nature of the lesions encountered in these patients. The reported cases of allergic encephalitis, myelitis and neuritis with serum sickness show considerable similarity to the nervous system reactions of acute virus exanthemata, infectious mononucleosis and collagen diseases.

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Sensitivity of Myasthenia Gravis Patients to Tubocurarine and Decamethonium

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THE earliest demonstration of a synergy between the pathologic processes in myasthenia gravis and the pharmacologic effects of a curare-like drug was provided by Kennedy and Wolf[1] and Harvey and Whitehill.[2] Quinine, in doses of from 300 to 600 mg. four times a day, was found to increase the symptoms of myasthenic patients; the quinine effect was reversed by neostigmine. The synergy was so well defined that Harvey and Whitehill proposed the use of quinine as a diagnostic test for the disease.

The synergy of curare with the disease was shown by Bennett and Cash[3] in 1943. Prompted by the gross similarity between signs of partial curarization and myasthenia gravis, they investigated the effects of intravenous administration of a purified curare extract (Intocostrin) in exaggerating the symptoms of the disease. Doses of Intocostrin equivalent to 7.5 to 15 microgm. of the alkaloid tubocurarine per kgm. of body weight produced effects in myasthenic patients comparable to those produced in normal subjects by doses ten to 20 times as large (150 microgm./kgm.). Administration of Intocostrin or tubocurarine under standardized conditions as described by Bennett and Cash is now an accepted, if somewhat hazardous, procedure used in the diagnosis of myasthenia gravis.[4] Patients with myasthenia gravis have also been found to be abnormally sensitive to the curarizing effects of 1, 2, 3-diethylaminoethoxy benzene triethiodide (Flaxedil), a synthetic muscular relaxant recently introduced into anesthesiology.[5]

Tubocurarine, Flaxedil, and quinine have in common a pharmacologic action at the neuromuscular junction to prevent depolarization of the muscle cell membrane by acetylcholine liberated from the nerve terminals. It would appear that patients with myasthenia gravis were abnormally sensitive to many, if not all, of the agents with such an action at the neuromuscular junction.

Decamethonium bromide, on the other hand, is a synthetic muscle relaxant

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TABLE 1

CHARACTERISTICS OF POPULATIONS OF NONMYASTHENIC SUBJECTS AND PATIENTS WITH MYASTHENIA GRAVIS

Characteristic	*Myasthenia Gravis*	*Normal*
Number of males	11	13
Number of females	19	9
Age in years (mean)	42	38
Range	(22-73)	(15-69)
Weight in kgm. (mean)	66	67
Range	(42-94)	(39-100)

with an action at the neuromuscular junction completely different from that of tubocurarine, Flaxedil, or quinine. Burns and Paton[6] have shown that decamethonium acts at the neuromuscular junction like an "unhydrolyzable acetylcholine" to produce depolarization of the junctional region of the muscle sufficient to prevent its responding by further depolarization to acetylcholine released from the nerve terminals. Paton and Zaimis,[7] and Scurr[8] have speculated on the sensitivity that patients with myasthenia gravis might show toward decamethonium, and have concluded that, in contradistinction to the response to tubocurarine, such patients should not be abnormally sensitive, but might be resistant to the paralytic effects of decamethonium. The clinical reports of Sellick,[9] Dundee and Gray,[10] and Churchill-Davidson and Richardson[11,12] seem to confirm these speculations, although the reports include no precise quantitative comparison of the sensitivities of the patients to the drugs.

The purpose of the experiments described below was to determine and compare equipotent doses of tubocurarine and decamethonium on normal subjects and on patients with myasthenia gravis. By interpreting the effects of these agents in the light of the difference in their mode of action at the neuromuscular junction, some insight might be gained into the pathophysiology of myasthenia gravis.

MATERIALS AND METHODS

Thirty patients with active myasthenia gravis, a diagnosis previously made on the basis of clinical course, response to neostigmine therapy, response to the intravenous neostigmine test,[13] and the intravenous curare test,[3] were selected at random and seen as outpatients. The group included both sexes, and various ages were represented (table 1). The known duration of the disease before these experiments were performed varied from a few weeks to more than 20 years. Neostigmine therapy was required by all patients and was adjusted by them according to their needs. Prior to the tests, neostigmine therapy was withheld for as long as was feasible; the time varied from three or four hours to several days. There was no uniformity of muscle groups affected among the patients, except that all of them complained of disturbed vision. Moderate hypertension existed in a few patients; otherwise, the

myasthenia gravis was uncomplicated by any other disease.

Fifteen non-myasthenic patients of various ages and both sexes were chosen at random from a general surgical ward; only one (a patient with thyrotoxicosis) had any presenting complaint related to weakness or fatigability of skeletal muscles. In addition, seven normal male volunteers were tested; some of them had been tested previously with tubocurarine and decamethonium by another technique. Since the "t" test indicated no significant differences in the data obtained from the two groups of non-myasthenic subjects, their data were pooled for the final calculations.

Neither the subjects nor the observer knew which drug was given during any given experiment. Data were used in the final calculations only when the subjects had been tested on successive days with tubocurarine and decamethonium (not always in that order), or on both of the days with tubocurarine.

All drugs were given intravenously into an antecubital vein by a timed interrupted infusion technique. Drug solutions were prepared from commercially available solutions (tubocurarine chloride pentahydrate, 3.0 mg. per cc.; decamethonium bromide, 1.0 mg. per cc.) diluted with 0.9 per cent sodium chloride solution. Tubocurarine was administered at a rate of 1.5 microgm. per pound per minute; decamethonium was administered at a rate of 0.75 microgm. per pound per minute. All drugs were given with standard 2 cc. and 5 cc. syringes.

With the subject in either a sitting or a reclining position, the grip strength of one hand was determined with a dynamometer calibrated in kilograms. At the time of each determination, the distance from the bridge of the nose to the near point of binocular convergence (NPC) was measured in centimeters. Ptosis, ability to swallow and phonate, facial expression, respiratory rate and amplitude, and posture were evaluated and recorded. Determinations of skeletal muscle strength were repeated at 45-second intervals before, during, and after the administration of the drugs.

After repeated determinations of grip strength and NPC yielded reproducible measurements, the drug was injected at a uniform rate for one minute. After a 20-second interval, a second injection was given over a one-minute period, and so on: a minute of injection alternating with 20-second intervals without injection. This timed interrupted infusion was continued until the time of the onset of paralytic activity had been reached, as signified by a doubling of the NPC. The quantity of drug administered at the time this end point was reached was considered to be the threshold dose of that drug in that subject. Most of the experiments performed on myasthenic subjects were terminated with neostigmine (0.25 to 0.50 mg.) given intravenously over a one-minute interval. Observations were continued with all subjects until grip strength and NPC had returned to control levels. All experiments were performed in the presence of an anesthesiologist equipped to perform endotracheal intubation and to supply positive pressure artificial respiration; his services were never needed.

Threshold doses of the drugs were expressed in micrograms per kilogram of body weight for each subject. For both groups of subjects treated with either of the drugs, the mean threshold dose and its standard deviation and standard error were calculated. Comparison between means was made by the "t" test.

For each group of subjects treated with one drug, the range between 0.01 microgm. per kgm. and the highest dose of the drug used with that group was divided into logarithmically spaced dose intervals similar to the division shown in figure 2. For each interval, the number of subjects whose thresholds were in that interval, and in all intervals smaller than it, was calculated. Each of these numbers was expressed as a per cent value of the total number of subjects in the group. When the empirical probits of these percentages were plotted against the logarithm of the highest dose in each dose interval, a statistically straight line was obtained. The equation of this log dose–cumulative effect curve was calculated by the method of least squares; the slopes of the line, its standard error, and the threshold dose of the agent required to produce an effect in 50 per cent of the subjects (TD50) were determined.

RESULTS

All experiments were performed without adverse effects on the subjects, all of whom were able to carry on their regular activities as soon as the experiment was finished. The incidence of effects, both symptomatic and objective, other than recession of the NPC, or slight changes in grip strength, seen with threshold doses of the two drugs is given in table 2; since the incidence of such effects in the myasthenic patients was not significantly different from that in the control group, only the total incidence is recorded.

TABLE 2

INCIDENCE OF EFFECTS OTHER THAN MEASURED MUSCLE PARALYSIS IN ALL SUBJECTS TESTED WITH THRESHOLD DOSES OF TUBOCURARINE AND DECAMETHONIUM

Side Effect	*Tubocurarine*	*Decamethonium*
Symptoms:		
Lightheadedness	9	13
Heavy eyelids	8	8
Blurred vision	5	9
Improved vision	2	8
Drowsiness	3	3
Feeling of warmth	1	2
Feeling of weakness in muscle groups other than eyes	6	1
Headache	0	1
Signs:		
Dysphonia	4	2
Dysphagia	1	1
Tachypnea	6	3
Improved skeletal muscle function	0	13
Cramping and muscle fibrillation	0	7
Total number of subjects	52	47

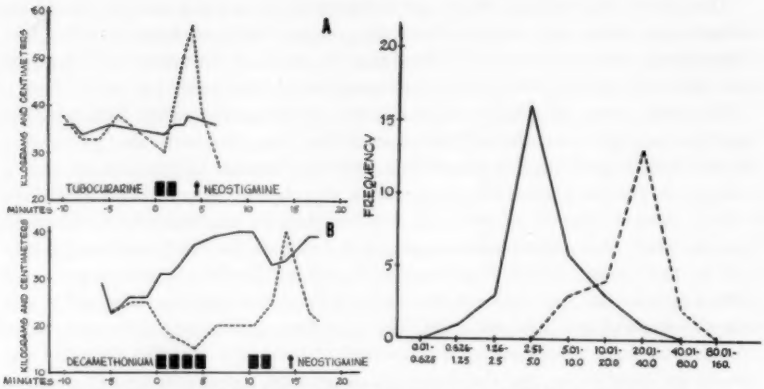

FIG. 1. (*left*) Course of minimal paralysis of extraocular muscles (NPC in centimeters: ----------) and muscles affecting grip strength (in kilograms: ——————) with tubocurarine (A) and decamethonium (B) in a subject with myasthenia gravis. At the times indicated by the bars, tubocurarine (1.5 microgm. per pound) or decamethonium (0.75 microgm. per pound) were injected; at the times indicated by the arrows, neostigmine (0.5 mgm.) was administered.

FIG. 2. (*right*) Frequency distribution curves of threshold doses of tubocurarine in myasthenic (——————) and non-myasthenic (----------) subjects. Threshold doses of tubocurarine in microgm./kgm. are plotted on the abscissa; frequency of observations is plotted on the ordinate axis.

Many of both the normal and myasthenic subjects interpreted the onset of action of both tubocurarine and decamethonium as a feeling of lightheadedness, never as vertigo. This sensation was succeeded by a "tired" feeling, as if the eyelids could be kept elevated only with great effort; increased ptosis was never noted objectively at this time. Soon afterward, the subjects complained of a blurring of vision and a feeling "as if I'd been reading a lot." At about this stage of curarization, increased ptosis was observed and the NPC began to recede. If the drug administration was continued, a feeling of lassitude was reported and relaxation was felt successively in the muscles of the jaw, neck, shoulders, and extremities. Concomitant with these sensations could be observed a gradual diminution of the facial folds, increased ptosis, progressive dysphonia of which the subjects never complained, an increased respiratory effort, and later, diminished grip strength and nodding of the head. Invariably, the sensation of drug effect in a muscle group preceded the appearance of a measurable weakness of the group. Ordinarily, curarization was not continued beyond the stage of minimal paralysis of the small muscles of the head. Figure 1A is a graphic demonstration of the time course of curarization of the extraocular muscles of a myasthenic patient and the characteristically rapid termination of the effects of both the drug and disease by the intravenous administration of neostigmine. In most cases the beneficial effect of neostigmine was observed from one to two minutes after the completion of the injection.

The extraocular muscles showed the greatest sensitivity of any muscle group to both tubocurarine and decamethonium in both normal and myasthenic

TABLE 3
THRESHOLD DOSES OF TUBOCURARINE, DECAMETHONIUM, AND ACETYLCHOLINE IN NORMAL SUBJECTS AND SUBJECTS WITH MYASTHENIA GRAVIS

Drug	*Subjects*	*N*	$\bar{x}$	*s*	*b*	s_b	*TD50*
Tubocurarine	Myasthenia gravis	30	5.42	4.19	3.254	0.164	3.80
	Normal	22	24.77	10.85	4.041	1.134	20.9
Decamethonium	Myasthenia gravis	25	5.53	3.18	2.951	0.317	4.97
	Normal	22	4.29	2.80	5.022	0.354	3.49
Acetylcholine*	Myasthenia gravis	20	367.5	111.0	8.872	0.542	322
	Normal	33	168.2	54.2	5.531	2.642	125

n = number of subjects
$\bar{x}$ = mean threshold dose (microgm./kgm.)
s = standard error of the mean
b = slope of the dose-effect curve
s_b = standard error of the slope
TD50 = median threshold dose (microgm./kgm.)
*Calculated from the data of Engbaek, L., EEG & Clin. Neurophysiol. 3:155, 1951. Doses of acetylcholine are total doses in micrograms.

subjects. In a few patients with myasthenia gravis affecting virtually only one group of muscles in addition to those of the eyes, i.e., pharyngopalatine muscles, lumbodorsal muscles, or the muscles of respiration, curarizing effects were noted in these groups simultaneously with the effects observed on the extrinsic ocular muscles and the levator palpebrae. Since all of the patients complained of blurring of vision, ptosis, or diplopia as prominent symptoms of the disease, it can be said that the muscles most affected by the disease were the muscles most sensitive to both curarizing agents.

The mean threshold dose of tubocurarine in patients with myasthenia gravis was about one-fifth of the mean threshold dose for normal subjects (table 3). The differences in the mean threshold doses of tubocurarine in the two groups was highly significant ($P < 0.001$), but inspection of the standard deviations of the means reveals that of every 100 normal subjects tested, three or four would have thresholds to tubocurarine which fell within the range of the responses of the patients with myasthenia gravis. Similarly, of every 100 patients with myasthenia gravis three or four would have thresholds within the normal range.

The median threshold doses of tubocurarine for the normal and myasthenic subjects bore the same relationship to each other as did the mean doses. The statistical identity of the slopes of the two dose-effect curves ($P > 0.3$) indicates that the distribution of sensitivities of the individuals in the two groups was the same in both.

Six subjects with myasthenia gravis were tested with tubocurarine on successive days. The mean difference in their thresholds to the drug in the two days (−0.033 microgm./kgm.) was insignificant ($P > 0.7$).

All of the effects of threshold doses of tubocurarine were reversed quickly by the use of neostigmine or of m-hydroxyphenyl-ethyldimethylammonium bromide (Tensilon) (5 to 10 mg.). The latter drug was found to be as effective as neostigmine in reversing the effects of tubocurarine in several of the myasthenic patients tested.

The severity of the disease could be gauged by the amount of neostigmine required by the patients with myasthenia gravis. In general, the lowest thresholds to tubocurarine were found in those patients who required the largest and most frequent doses of neostigmine. Severity of the disease tended to correlate inversely with the threshold to tubocurarine.

In contrast to tubocurarine, decamethonium did not invariably produce progressive paralysis. In 13 of the 25 myasthenic patients studied, paralysis was preceded by a transient period of remission of myasthenic symptoms and signs, which disappeared as the drug infusion was continued (figure 1B). In such patients the distance to the NPC was diminished, ptosis was lessened, grip strength frequently increased, and the patients usually made comments in surprise such as: "I feel better instead of worse." or "Are you giving me prostigmine?" In no case of myasthenia gravis did this amelioration of symptoms and signs persist after termination of the experiment. The phenomenon was never observed in the non-myasthenic subjects.

In seven of the myasthenic patients, only three of whom were even transiently benefited by the decamethonium, fibrillatory movements in muscle groups, slight involuntary movements of the extremities, and cramping sensations in muscle groups were observed and reported. These effects were most likely to occur in muscle groups immediately after they were exercised: periorbital muscles, muscles of the forearm after the determination of grip strength, the muscles of the calf and the quadriceps on arising, or walking, and so on. Spontaneous nystagmus was never observed. Fibrillatory and involuntary movements were abolished by continuing the drug infusion; cramping after exertion usually persisted even after the experiment had been terminated. Subjectively, these sensations and movements were characterized by the patient who said, "I feel tense and jumpy; it's like I took too much prostigmine." These effects were never observed in the normal subjects with the doses of decamethonium used, although such effects have been noticed in normal subjects given larger doses.[14]

Neostigmine (0.25 to 0.50 mg.) was given intravenously to many of the myasthenic patients after they had received a threshold dose of decamethonium. Under these conditions neostigmine did not increase paralysis as might have been expected, but rather diminished it.

The mean threshold dose of decamethonium for the subjects with myasthenia gravis was slightly and insignificantly higher than the threshold for the non-myasthenic subjects ($P > 0.8$) (table 3). Median threshold doses for the two groups bore the same relationship to each other as did the mean threshold doses. No significant difference was demonstrable between the slopes of the dose-effect curves for decamethonium in the two groups ($P > 0.7$); as was the case with tubocurarine, the distribution of sensitivities of the patients with myasthenia gravis to decamethonium was the same as the distribution of sensitivities of normal subjects to the drug.

DISCUSSION

Critique of method. Valid interpretation of the results of pharmacologic analyses of the effects in myasthenic and normal subjects of drugs with actions at the neuromuscular junction is contingent on certain restrictions in the design of the experiments. First, the dose-effect curves of any one drug in both normal and myasthenic subjects should be parallel in order that comparison of effects in the two groups can be made at all dose levels (table 3). In both groups of subjects, increments of dose should be equal between any pairs of doses, in order that the dose effect curves might be a continuum of both dose and effect; in the experiments reported here, this was accomplished by division of the total dose range into logarithmically spaced intervals. Second, the drugs should be selective for the neuromuscular junction and specific in their actions on it. If this condition cannot be fulfilled (as is the case with most drugs) the drugs should be used in quantities just large enough to produce neuromuscular effects, but so small as to minimize the number and the intensity of side effects. In practice, this consists of finding the threshold dose of the drug to produce effects on the neuromuscular junction. Third, sufficiently large groups of subjects and sufficiently precise and objective end points must be used to permit statistical evaluation of the experimental results. Finally, whenever two or more drugs are to be tested, at least two should be tested in each subject.

The duration of the infusion was always shorter than the duration of action of a single injection of either of the drugs. It has been shown that the duration of action of a single dose of tubocurarine five times that used in the normal subjects was about 25 minutes, or roughly two and a half times the duration of the longest experiments with tubocurarine reported here.[14] The duration of action of decamethonium in single doses about six times greater than those used in either the myasthenic or normal subjects was about 15 to 20 minutes, or about three times the duration of the experiments with decamethonium in this series.[14] The use of the timed interrupted intravenous infusion technique probably gave a valid and reliable estimate of the threshold doses.

The possible effects of spontaneous variations in the severity of myasthenia gravis on the results of the tests was circumvented by testing patients on successive days. The transient effect of even the longer acting tubocurarine and relative constancy of the threshold to the drug on successive days is indicated by the insignificant differences in threshold to the drug obtained in the six patients tested with the drug on consecutive days.

Throughout this study paralysis of the extraocular muscles was the criterion of drug effect. The measurement of the action of tubocurarine and decamethonium on the extraocular muscles is a valid estimate of their effect at the neuromuscular junction. Drucker et al.[15] have demonstrated that the only effects of these drugs on vision is a result of action at the skeletal neuromuscular junction; accommodation, visual acuity, color vision, intraocular tension, and pupillary constriction and dilatation were unaffected by doses of these highly selec-

tive drugs in doses five to 25 times larger than those used in this study. On the other hand, sensitivity of the extraocular muscles to one of the agents in any individual need not always be a reflection of the sensitivity of other muscle groups in that subject. One of the normal subjects tested was found to have extraocular muscles sensitive to a dose of tubocurarine (8.0 microgm./kgm.) which caused an effect in two-thirds of the myasthenic subjects studied. However, the muscles of the forearm and of respiration in this subject were not abnormally sensitive to tubocurarine as determined by another method.[16]

Sensitivity of the subjects to tubocurarine and decamethonium.

The smallest dose of tubocurarine which had a measurable effect on the muscles of non-myasthenic subjects affected the extraocular muscles. The range of these threshold doses of tubocurarine in the non-myasthenic subjects was between 7.1 and 46.2 microgm./kgm. This range agrees well with the data published by Jarrett et al.[17] on the dose range of tubocurarine that affected ocular convergence in normal subjects: 8.25 to 33.00 microgm./kgm. The extraocular muscles of non-myasthenic subjects were 5.8 times as sensitive to decamethonium as they were to tubocurarine; in assessing the effects of the same drugs on the muscles which control grip strength, decamethonium was found to be 4.8 times as potent as tubocurarine in normal subjects.[14]

The threshold dose of tubocurarine in myasthenic patients, as determined by the timed intravenous infusion technique (5.42 microgm./kgm.) is to be compared with the fixed dose of curare (equivalent to 7.5 microgm./kgm. of tubocurarine) recommended by Bennett and Cash for use in the diagnostic test for myasthenia gravis. The effects of the threshold dose were much less severe than those reported by Bennett and Cash with the single injection of the larger dose, and the threshold determinations were less unpleasant to all of the patients we studied than were their previous diagnostic curare tests.

The mean threshold doses of tubocurarine in myasthenic and non-myasthenic subjects were significantly different. However, the sensitivity of any individual to the drug does not, by itself, characterize the subject as "normal" or "myasthenic," since the ranges of the threshold doses in the non-myasthenic and myasthenic subjects, respectively, are not mutually exclusive. The frequency distribution curves of the threshold doses of tubocurarine in the individuals in the two groups overlap (figure 2). Since 3 or 4 per cent of normal individuals will have a "myasthenic" response to tubocurarine and about the same proportion of patients with myasthenia gravis will have a "normal" response to minimally effective doses of the drug, it is probable that the anesthesiologist will encounter three or four cases of abnormal sensitivity to tubocurarine out of every 100 presumably normal patients. This fact emphasizes the necessity of testing patients with small doses of curare before anesthesia is begun, in spite of the limitation imposed on the interpretation of the results of the test in any one individual.

The absence of sensitivity of the myasthenic patients to decamethonium suggests that use of this drug may be indicated in patients sensitive to tubo-

curarine to whom a muscle relaxing agent must be given. Use of decamethonium under such circumstances should be made with the knowledge that the duration of action of the drug is shorter than that of tubocurarine, that decamethonium produces more respiratory depression with equal muscular relaxation than does tubocurarine, and that abnormal responses to repeated doses of decamethonium may occur.[18]

Pathophysiology of myasthenia gravis.

The results of neurophysiologic and pharmacologic investigations demonstrate the involvement of the skeletal neuromuscular junction in the pathologic state of myasthenia gravis.[19,20] This state may be described as one in which insufficient acetylcholine is released from the motor nerve terminals to invoke a muscular contraction. Three factors, or a combination of them, could readily alter the sensitivity of the muscle to nerve stimulation. Acetylcholine might be synthesized by the nerves in quantities inadequate to produce contraction of a muscle of normal sensitivity. Excess tissue cholinesterase might destroy acetylcholine produced in normal quantities before it could affect the muscle. Some material or process might interpose itself between normal nerve terminals and normal muscle end plates and increase the threshold of the muscle to acetylcholine present in quantities normally adequate for neuromuscular transmission. The last is the condition which occurs during paralysis produced with tubocurarine. No evidence exists that tissue cholinesterase is increased in amount in patients with myasthenia gravis.[21,22]

The similarities between manifestations of myasthenia gravis and those of curarization have been summarized and discussed by Harvey and Lilienthal.[16] The sensitivity of patients with myasthenia gravis to tubocurarine is consistant with the idea that an abnormal curare-like substance may be present at the neuromuscular junctions of the patient. The responses of normal and myasthenic subjects to decamethonium are also those which might be expected if a curarizing substance were present in patients with myasthenia gravis. It is well known that administration of a curarizing agent of the type of tubocurarine, antagonizes the paralytic effects of a subsequent administration of decamethonium.[23] The higher mean and median threshold doses of decamethonium in the myasthenic patients, as compared to the normal subjects, may be an example of this phenomenon, even though the differences are statistically insignificant. Under appropriate circumstances, it is also possible to show an antagonism of a dose of decamethonium to a previously administered dose of tubocurarine and tubocurarine-like agents;[24,25] as the dose of decamethonium is increased paralysis supervenes, even in the presence of tubocurarine. The amelioration of the signs and symptoms of myasthenia gravis, and the subsequent paralysis, by progressively larger doses of decamethonium would appear to be the clinical counterpart of this effect. The mechanism by which decamethonium antagonizes tubocurarine, or a curare-like substance which might be present in myasthenia gravis, is unknown. It is conceivable that decamethonium has its effects by virtue of its properties as an "unhydrolyzable acetyl-

choline" to stimulate skeletal muscle directly. On the other hand, decamethonium has been reported to have potency as an anticholinesterase drug roughly 1/100 that of neostigmine.[16]

The presence of a substance in the plasma of patients with myasthenia gravis which had the ability to block neuromuscular transmission, first reported by Wilson and Stoner,[26] has not been confirmed by the work of McEachern,[27] Cohen et al.,[28] or Buchtal and Engbaek.[29]

It would be difficult to determine directly whether patients with myasthenia gravis suffer from an inability to synthesize sufficient acetylcholine to stimulate skeletal muscle, or whether the threshold of the myasthenic muscle is elevated to acetylcholine released from nerve endings in normal quantities.[30] A critical indirect experiment designed to resolve the problem is to determine and compare the thresholds of myasthenic and normal muscles to exogenous acetylcholine, administered intraarterially. Lanari[31] and Harvey and Lilienthal[20] used relatively large doses of acetylcholine in such an experiment and concluded that the muscles of myasthenic patients were more sensitive to acetylcholine than were the muscles of normal subjects. In normal individuals the drug produced paresis of the muscles affected, whereas in myasthenic patients, it produced strong muscular contractions. If, in a myasthenic patient, a curarizing substance were present at the neuromuscular junction, large doses of acetylcholine might be required to antagonize the curare-like substance and produce a muscular contraction equivalent to that which might be produced in a normal subject with a far smaller dose of the drug. Excess acetylcholine at the normal neuromuscular junction is known to produce "curare-like" effects. Hence, the results of Lanari and of Harvey and Lilienthal do not preclude an elevated threshold of myasthenic muscle to acetylcholine. Acheson et al.[32] and Wilson and Stoner[33] performed similar experiments using smaller quantities of acetylcholine, but because of the variability of the thresholds in the small number of subjects studied, and the difficulty in finding true threshold doses, they concluded only that the muscles of myasthenic patients were not more sensitive to acetylcholine than the muscles of normal subjects.

Engbaek[34] determined and compared the threshold doses of acetylcholine injected rapidly into the brachial artery in 33 normal and 20 myasthenic subjects. Since the data are published only in tabular form, we have taken the liberty of recalculating Engbaek's data in exactly the ways described for determining the mean and median threshold doses of tubocurarine and decamethonium. In recalculation, we considered the threshold dose of acetylcholine in any given subject to be the largest dose tested by the author, at which no response was obtained. The mean and median threshold doses of acetylcholine in myasthenic subjects were more than twice as large as the mean and median threshold doses in the normal subjects (table 3); the differences in the means is highly significant ($P < 0.001$). The muscles of patients with myasthenia gravis were less sensitive to acetylcholine than the muscles of normal subjects when threshold doses of the drug in the two groups were

compared. The slopes of the dose-effect curves for the two groups were insignificantly different ($P < 0.2$); the only difference between the curves was the difference between their intercepts. This is precisely the effect of substances like tubocurarine on the dose-effect curve for acetylcholine when the effects of acetylcholine are antagonized in isolated muscle preparations.[35,36]

The experiments reported here do not refute directly the concept that patients with myasthenia gravis are unable to synthesize and release adequate amounts of acetylcholine at their neuromuscular junctions.[37,38] There is no evidence, however, that acetylcholine synthesis in the autonomic nervous system is qualitatively or quantitatively different from acetylcholine synthesis at the skeletal neuromuscular junction, and, typically abnormal function in myasthenia gravis is confined to the skeletal neuromuscular junction. None of the patients studied in this series complained of dysfunction of muscles other than skeletal muscles. Pupillary reflexes were active and intact; constipation was not a prominent feature; reflex pulse and blood pressure changes were normal.

All of the results of pharmacologic analyses of neuromuscular function in patients with myasthenia gravis support the contention that a fundamental feature of the disease is the failure of synaptic transmission at the skeletal neuromuscular junction. The process acts in a manner analogous to that of tubocurarine in selectively decreasing the muscular response to acetylcholine.

SUMMARY

1. Threshold paralytic doses of tubocurarine and decamethonium were determined in 30 myasthenia gravis patients and 22 non-myasthenic subjects.

2. Patients with myasthenia gravis (mean threshold dose 5.42 microgm./kgm.) were 5.5 times as sensitive to tubocurarine as were non-myasthenic subjects (mean threshold dose 24.77 microgm./kgm.).

3. About 3 to 4 per cent of normal subjects are as sensitive to tubocurarine as an average patient with myasthenia gravis. About 3 to 4 per cent of patients with myasthenia gravis are not abnormally sensitive to threshold doses of tubocurarine.

4. Patients with myasthenia gravis were not more sensitive to decamethonium than were non-myasthenic subjects. With subthreshold doses of decamethonium, patients experienced transient amelioration of signs and symptoms.

5. Results are consistent with the concept that the fundamental feature of myasthenia gravis is a blockade of the neuromuscular junction by a substance or process which decreases the muscular response to acetylcholine.

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Occurrence of "Continuous Symptoms" in Epilepsy Patients

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It is an observation of long standing that some people with epilepsy are frequently more comfortable when having attacks than when they are free of seizures. Sir William Gowers appears to have been one of the first clinicians to have speculated on the mechanism of this phenomenon, concerning which he wrote as follows:[1]

"When attacks that have occurred for many years, stop suddenly, whether the stoppage is spontaneous or due to the influence of drugs, patients may become dull, forgetful, sometimes irritable and sometimes half idiotic. The effect is often ascribed to the remedy used, especially if this is bromide; but it seems to be due rather to the general depression of cerebral function by the condition of the nerve cells, which by repeated discharge, have developed a tendency to overproduction of nerve-force, and this is no longer released in fits. A fit may completely remove the state. It is common for patients to say that they feel better when they are having fits than when they are not."

We have been impressed by the frequency with which the patient's complaints under these conditions may resemble pre-existing aura. For this reason we have described such reactions under the term "continuous aura," rather than as non-ictal disturbances, since there seems reason to suspect that the mechanism which produces the seizure may also be responsible for the prolonged reaction.

An exact analysis of the frequency of such "continuous symptoms" proved to be impossible, since there was no clearcut dividing line between cases in which the complaints were clearly related to the pattern of the usual seizures and those in which there was question as to whether they resulted from an unassociated condition, such as a specific drug intolerance or a psychoneurosis. However, a review of the records of 100 consecutive patients in whom the medical control of seizures had been attempted during 1951 showed 12 cases

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which appeared to fall into this category, the symptoms resembling a "continuous aura," of which the following case histories represent typical examples.

CASE REPORTS

Case 1.—A married woman aged 25 had no family history of seizures. When five years old, she had a generalized convulsion lasting several hours during an undiagnosed febrile illness. She recovered with no obvious sequelae and was free of seizures until the age of 16, when she began to have both grand mal and psychomotor attacks. These were preceded by an aura of numbness in the right hand, followed by dizziness, aphasia and loss of consciousness. The major seizures, which only occurred about once a year, commenced with jerking in the right hand. The psychomotor seizures consisted of automatisms lasting several minutes, during which she often carried on activities in an apparently normal manner. Neurologic examination was within normal limits, but an electroencephalogram showed a left temporal spike discharge, with some associated focal slow-wave activity.

The addition of 0.1 gm. Mesantoin (3-methyl-5, 5 phenylhydantoin) to her previous daily medication of 0.2 gm. Dilantin (diphenylhydantoin) and 0.1 gm. phenobarbital was followed by changes in the seizure pattern. Initially psychomotor seizures decreased in duration but increased in frequency until she was having "too many to count." The dosage of Mesantoin was then increased to 0.2 gm. daily, without changing the other medications, following which she said that these attacks had been strikingly reduced in number and occurred at about weekly intervals. However, she now complained of "a numb weak feeling" in her right hand, which, she said rendered her hand "useless," though it was not objectively weak or clumsy, and sensory loss could not be demonstrated. At this time another electroencephalogram was recorded which showed the spike discharge to be still present and possibly more active. With continued medication at the same dosage, the hand sensation gradually diminished in intensity.

Case 2.—A 20 year old girl had been having grand mal convulsions every one to three months for the past five years. The only aura was a momentary "blanking of the mind," and neither the generalized tonic-clonic convulsions nor the sequelae showed any focal features. She also complained of momentary "flashes of blank-mindedness" which occurred almost daily. No family history of seizures could be elicited, but she had had convulsions accompanying infectious fevers on two occasions in early childhood.

She had previously taken 0.3 gm. Dilantin daily, but had stopped because it had not controlled her seizures, and because of her complaint of "a creeping sensation under the skin" in her right side while taking this medication. Phenobarbital was substituted, resulting in some reduction in the frequency of attacks. She also became aware for the first time of a movement of the right leg and her head, she thought to the right, at the onset of her attacks. Physical examination showed no abnormality, but an electroencephalogram revealed very active spike discharges in both temporal regions. It was not possible to ascertain whether more than one focus of abnormal activity was present. A combination of 0.3 gm. Dilantin and 0.1 gm. phenobarbital daily was prescribed, as she had not previously taken these drugs together.

A month later she said that she had had no seizures, but complained bitterly of various visceral sensations which she had not had previously, but which now bothered her continuously. These were described as epigastric discomfort, with frequent belching and bloating and a painful "lump in the throat," often so severe that she could hardly get her breath. She also complained of waves of chilly sweat passing over her hands.

The electroencephalogram was repeated and showed a persistent active disturbance of the type noted previously. Dilantin was stopped and she was given 0.16 gm. phenobarbital in the morning. Four days later she had another seizure and was dramatically relieved of her abdominal and other somatic complaints.

Case 3.—A 35 year old housewife had been having frequent automatisms and occasional generalized convulsions since she was in her teens. The etiology of these attacks was unknown. Her electroencephalogram showed a rather clearcut and active left temporal spike focus, but clinical examination revealed nothing abnormal.

The psychomotor seizures, which occur almost daily, were ushered in by an aura of an indefinable sense of dread and terror, accompanied by a feeling that she had left undone something she ought to have done, following which she lost consciousness. The attack was accompanied by a staring expression, smacking of the lips and some simple repetitive hand movements. Subsequently, she often had automatisms lasting several minutes, during which she might continue her activities in an apparently normal manner. She also described momentary "flashes" of causeless terror similar to, but briefer than her aura, occurring several times a day.

Dilantin and Mesantoin combinations have reduced the incidence of her attacks by about one third, but if the seizures are suppressed she complains of an almost continuous feeling of dread and anxiety. When seen in this state she exhibits an attitude of tortured self-concern with great apprehension, saying that though she knows it to be unreasonable she feels that something terrible is going to happen to her. This state has never lasted longer than ten days when either deliberately or through confusion, she omits her medication, has a seizure and feels considerably relieved, saying that "the tension lifts off like a weight." So far it has not been possible, because of her restlessness, to obtain a technically satisfactory electroencephalogram during this reaction.

DISCUSSION

The following features were noted in the group of patients developing such continuous symptoms:

1. *Type of convulsive disorder.* Although every patient in this group did not show a clearly localized focus on electroencephalography, none showed patterns suggesting an idiopathic type of disturbance. In the subjects showing clearly focal lesions, temporal lobe spike discharges were most commonly seen. The etiology of the disorder was uncertain in most instances, but seemed to fall into no single pattern. Patients in whom seizures were symptomatic of an actively progressive disorder were excluded from this series.

2. *Nature of the symptoms.* The "continuous symptoms" observed usually resembled the patient's characteristic aura, which were most commonly of the type which Hughlings Jackson[2] termed "crude sensations" and "dreamy states." In some instances (case 2), a patient who had prevously had little or no warning of an impending attack developed an aura when taking medication, and later complained of prolonged symptoms resembling this sensation.

Though the most frequent complaints were of visceral sensations and psychic states, somatic sensations were also reported (case 1). We have recently observed a subject in whom there were prolonged motor manifestations related to the seizure pattern. This patient, whose electroencephalogram shows evidence of a focal lesion of the medial aspect of the right frontal lobe, had become mentally disturbed, with confusion and irritability, on more than one occasion following successful control of her seizures with anticonvulsant medication. When this treatment was stopped, she developed almost continuous twitching movements of the left facial muscles. This persisted for 36 hours at which time she had a seizure, following her usual pattern of contralateral

tonic-adversive movements, preceded by left sided facial twitching, after which she was much more alert and cooperative.

We have been particularly impressed by the frequency of psychiatric states as a "continuous symptom" and the similarity of this reaction to the "psychoses" described in patients taking anticonvulsant drugs. The latter have been discussed by Gibbs[3] who remarks that the psychosis seen as a complication in the treatment of psychomotor seizures with Phenurone (phenacemide) is probably similar in mechanism to the psychic disorders which may occur when such seizures are suppressed by other anticonvulsant agents. Perhaps a "continuous psychic aura" could be responsible for the disturbance in both instances.

3. *Effect of medication.* Because of the fact that phenomena of the type described were not drug specific, it was felt that these observations support the impression that the symptoms were a manifestation of a change in the activity or spread of the epileptic process. They did, however, appear to be more prominent in patients controlled principally by anticonvulsants of the hydantoinate group, than in those taking barbiturates alone. These observations find hypothetical support in Williams'[4] summary statement that the sedative anticonvulsants protect the brain from the epileptic disturbance, while the hydantoins directly inhibit the epileptic process without depressing cerebral activity. Recent experimental work[5] on the seizure mechanism and the mode of action of anticonvulsant drugs suggests possible neuronal mechanisms by which an epileptic focus could be the source of disturbance which might influence the function of the nervous system as a whole, even in the absence of a manifest seizure.

In several instances the "continuous symptoms" appeared as a transient condition following a change of medication, diminishing and eventually disappearing if the patient persisted with the new treatment regimen.

4. *Electroencephalographic observations.* No outstanding difference has so far been noted between electroencephalograms made during the complaint of "continuous symptoms," and those obtained at other times; in particular no significant change in the incidence of focal spike activity has been seen. This is in keeping with Gibbs'[3] experience, as he comments that non-ictal psychiatric symptoms of psychomotor epilepsy are not concomitant with, nor immediately evidenced by, electroencephalographic abnormalities.

There are of course formidable difficulties in the evaluation of such serial electroencphalographic studies, both in the presence of generalized changes in the record due directly to the drugs employed and in reproducing the conditions under which the initial tracing was made. The latter proved particularly difficult in the present subjects, as the "continuous symptoms" themselves prevent relaxation of the patient, which, by its effect on arousal mechanisms, may produce changes in the electrical abnormality[6] of an order sufficient to mask small changes in the record. Also the finding that seizure activity may be ushered in by a flattening of the electroencephalogram (which Jasper[7] has termed "suppression") indicates that changes in background activity have

to be considered as well as the appearance of abnormal features. In this connection the observation of Toman,[5] based on direct oscillographic records from the region of a focal lesion, that the onset of a seizure disturbance may be associated with high frequency electrical discharges of the order of 1000 cps, may indicate inherent limitation in our present recording techniques in that such frequencies as the latter lie far outside the parameters of response of standard recording instruments.

SUMMARY

1. Certain patients with convulsive disorders develop a type of prolonged, non-ictal symptoms during medical treatment. This reaction appears to be related to the cerebral mechanism producing seizures and has been thought to represent a continuous aura. This impression is supported by the presence of one or more of the following findings:

The appearance of symptoms resembling the characteristic aura.

The appearance of symptoms related to the known function of a cortical area in which a focal electrographic disturbance can be demonstrated.

The disappearance, or marked modification, of symptoms following the occurrence of a seizure.

2. This type of reaction was seen in patients showing clinical and/or electroencephalographic evidence of focal brain lesions which were not progressive during the period of observation, most commonly involving the temporal lobes. The symptoms fell into three groups:

Visceral symptoms, which frequently resembled a psychoneurotic reaction.

Psychiatric symptoms, which included both affective and intellectual disturbances.

Somatic sensations and motor phenomena, which were rare.

3. The reactions were not drug specific, though not prominent in patients controlled predominantly with phenobarbital, and often appeared to represent a transient phase during the course of therapy.

4. Possible mechanisms are discussed and the suggestion is made that the concept of a continuous "intellectual" or affective aura, may offer a clue to the problem of the epileptic who becomes psychotic during drug therapy.

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Effect of Tensilon in Myasthenia Gravis

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TENSILON, or 3–hydroxy phenyldimethylethylammonium chloride, is one of the quaternary ammonium salts which have been shown to exert a direct stimulatory effect on the neuromuscular junction.[1–4] An outstanding property of this substance is its ability to antagonize the neuromuscular blockade produced by d-tubocurarine. As the potency of this compound is much greater at the neuromuscular junction than at other cholinergic sites, its anticurare action in animals and man[5] is accompanied by only minimal undesirable cholinergic effects. It has already been shown that the organic phosphates, such as tetraethylpyrophosphate, act only by their anticholinesterase effect; that neostigmine has both a direct stimulating effect at the myoneural junction and an anticholinesterase effect; and that Tensilon acts primarily by direct stimulation at the myoneural junction and only secondarily as an anticholinesterase agent. The last named drug is essentially similar to neostigmine in its structure, but has one less radical, the carbamate ester, which is apparently responsible for the main anticholinesterase action.

Macfarlane, Pelikan and Unna[6] first reported the beneficial effect of intravenous use of Tensilon in a child with myasthenia gravis. Ten mg. brought prompt though transient improvement in strength, as well as the alleviation of ocular signs in this child.

The present series includes a total of 13 patients with myasthenia gravis and four controls, all of whom were given Tensilon. Four of these patients have been described in detail previously.[7] All had intravenous injections of 10 or 15 mg. of the drug each; three received additional dosages orally, while one patient also had intramuscular injection of the drug. All patients were examined by more than one examiner before testing, with efforts being made to establish objective findings for comparison. The Lawton dynamometer was used to measure grip-strength in pounds. Blood pressure and pulse rates were

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also determined during the course of the experiments. Most patients were tested while in the recumbent position.

The first side effects of intravenous treatment were lacrimation, distorted vision, and a cramping sensation in the eyes and lids. However, these did not cause any of the patients serious discomfort and lasted for only a minute. Increase in strength began within 30 seconds, or as soon as it could be tested in most patients, and increased to a maximum within one to ten minutes. In all patients strength began to decline after ten minutes, but there was a secondary rise of lesser degree. The total effect of the injection lasted less than one hour in most patients. Grip-strength increased from 90 to a maximum of 200 pounds in the patients with myasthenia gravis. Several patients who could not move the indicator on the dynamometer at the beginning of the test were able to achieve over 100 pounds within 60 seconds. Clinical improvement correlated favorably with this and was sometimes spectacular. For example, one patient, who had atrophy of both quadriceps and had no power to extend the leg when given maintenance dosages of neostigmine, was found to have complete range of active movement after injection. Another patient with myasthenia gravis, who had been admitted to the hospital with respiratory infection and inability to clear her throat of tenacious sputum, showed prompt improvement after a 10 mg. intravenous injection.

Side effects of administering the drug intravenously were mild. No patient with myasthenia gravis had fasciculations, though the control group did experience them. Gastrointestinal stimulation did not occur in all patients; even when it did, it was fleeting and of slight degree. No instance of pronounced bradycardia occurred. Blood pressure fell a maximum of 10 mm. Hg systolic and 8 mm. Hg. diastolic within one to ten minutes. Some patients felt a vague type of dizziness, but no other symptom of cerebral stimulation was noted.

There was an improvement in strength regardless of the medication taken before the test, but the increase seemed to be greater in those who took the tetraethylpyrophosphate than in those who were being maintained on adequate doses of neostigmine. In one test, 6 mg. of the drug produced a response of slightly greater magnitude and of more rapid onset than did 1.5 mg. of neostigmine given intravenously. Like neostigmine and acetylcholine, Tensilon has been shown experimentally to have a curarizing effect when given in excessive amounts. This finding was verified clinically when one patient became very weak and aphonic and had respiratory embarrassment from an overdosage. These effects wore off in less than an hour, however.

It was interesting to observe that the control subjects also experienced a prompt increase in strength even though it was of very small magnitude and that they revealed the same pattern of drop with secondary rise over a period of 30 minutes. The secondary rise noted in most tests may represent the minor anticholinesterase action of the drug. In general, the side effects were more pronounced in the controls than in the patients with myasthenia gravis.

One of our series, a 61 year old myasthenic male who had undergone a

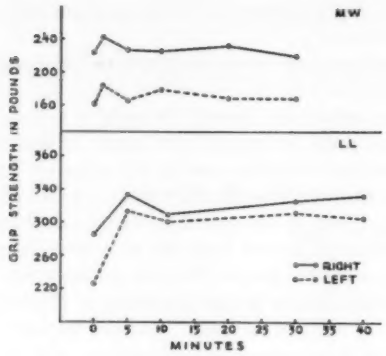

FIG. 1. Upper chart shows response in grip strength to 10 mg. Tensilon of control subject M.W. Lower chart shows the response of patient L.L. with myasthenia gravis to 10 mg. Tensilon.

thymectomy, had been maintained for three years on phosphate therapy; his response to intravenous administration of Tensilon was comparable to those of the other patients. He was later hospitalized and taken off all medication for the purpose of evaluating his response to intramuscular injections. At different times he was given doses of 10, 25, 50, 75, and 100 mg. intramuscularly. All were followed by increased strength as manifested by clinical examination and grip-strength as measured by the dynamometer. The response became apparent within ten minutes, attained the maximum in about an hour, and then declined over a period of three to five hours. Injections of 25 and 50 mg. produced the greatest increase in strength; injections of 10 or 100 mg. gave the least. A secondary rise did occur, was usually moderate, and seemed to be no greater with 100 mg. than with 50. Strength was fairly well maintained by injections of 50 mg. every three to four hours. Control saline injections failed to produce any increase in strength.

Reactions to the intramuscular medication, which began with a dose of 25 mg., were minimal, and consisted of slight dizziness, blurring of vision, and loose stools. At the 75 mg. dosage, the patient had some abdominal cramping, which was readily relieved by oral atropine.

The patient was then given Tensilon orally in a 5 per cent solution; again a definite measurable increase in strength resulted from the oral administration of 50 to 250 mg. doses. The effect began within 30 to 60 minutes and lasted several hours. The drug was then given to the patient orally while at home under more demanding circumstances. Although each time it gave him an increase in strength, it was not satisfactory in the dosage used. The patient discontinued the medication because of headaches he had experienced during its use.

CONCLUSION

Tensilon seems to offer a new approach to the study of myasthenia gravis, based on pharmacologic action unrelated to anticholinesterase activity.

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Most writers on megrim are agreed that even in those cases where the attacks have commenced early, and persisted in a severe form through the greater part of life, they are generally found to abate when the patient attains the age of fifty or thereabouts, and cease completely before old age. It is in fact comparatively rare to meet with old people who suffer from this malady. Sometimes the spontaneous decline takes place much earlier. In prolonged cases a maximum of severity is often attained about the age of thirty, and it is not uncommon for people of that age to seek medical advice in consequence; this will be apparent by reference to the second column of ages in the table of cases, and it has also been noticed by Labarraque.

Tissot observes on this subject:—"The affection continues in full force up to the age of fifty-five or sixty; then, generally, the paroxysms become feebler, wider apart, and almost invariably before the age of seventy the attacks have become very slight. With women the seizures often become more frequent towards the period of the suppression of the catamenia, and diminish again when the critical period has passed. The affection follows a nearly uniform course in each individual, and with all it is ordinarily less violent at the commencement, becoming more so at the end of a few years. It persists at the same intensity for a certain time, gradually declining afterwards, but with this exception it varies much in different individuals." "Sometimes," says M. Piorry, "Migraine is cured spontaneously with advancing years, but often also the paroxysms of which it consists become more and more frequent and render existence deplorable." This last observation is true no doubt of the worst cases in middle age, and under aggravating circumstances to be mentioned by and by, but it is quite contrary to my experience of the usual course of the malady in the decline of life.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Philip J. Vogel, M.D.
and Cyril B. Courville, M.D.

PRESENTATION OF CASE

A 69 year old man was admitted to the White Memorial Hospital on April 17, 1952, with the history of severe headaches and dizziness since an auto-train collision about two months previously. The headache became progressively more disabling and on the morning of admission it was so severe as to be uncontrollable by ordinary analgesics. He became stuporous rather suddenly and was sent to the hospital by his private physician.

On examination the patient was comatose and could not be aroused for questioning. The pupils were equal, but reactionless. A bilateral papilledema was found to be present. Moderate rigidity of the neck on flexion, a generalized areflexia and bilateral Babinski signs were the only objective significant findings on neurologic examination. The blood pressure was 146 systolic, 68 diastolic, the pulse rate 80 and respirations 18 per minute. No evidence of visceral disease was noted.

A diagnosis of chronic subdural hemorrhage was made and the patient taken to the operating room within an hour and a half after admission. A bilateral subdural hematoma with a liquid content was evacuated, first on the left and then on the right. The brain was markedly compressed, more on the left side, and the cortex did not resume its normal position during the period of operation.

The patient gradually regained consciousness, became mentally alert and cooperative, and was able to take nutrition by mouth. One week after surgery, he again complained of headache and the following day was found to be lethargic. Examination disclosed a left hemiplegia with typical reflex responses on this side. It was presumed that this episode was due to an internal thrombosis of some branches of the right middle cerebral artery. A lumbar puncture disclosed the fluid to be clear and under a pressure of 420 mm. The patient remained comatose with an elevated spinal pressure between 450 and 180 mm. on daily taps made during the next ten days.

In spite of all efforts, the patient remained in a stuporous state with only minor fluctuations in his state of consciousness. He was discharged to his home, completely helpless and vegetative, on June 8, 1952. The diagnosis on discharge included bilateral subdural hematomas, right-sided cerebral thrombosis, postoperative cerebral edema, and probable residual encephalopathy consequent to chronic subdural hematoma.

At home he continued in the state of lethargy and inanition without improvement. The course was progressively downhill and he died at his home on September 19, 1952.

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CLINICAL DISCUSSION

DR. VOGEL: The clinical diagnosis of the causative lesion in this case is quite incidental. The development of signs of increased intracranial pressure leading to coma following an injury to the head some seven weeks prior to the patient's admission to the hospital were characteristic of a subdural hematoma. The findings on examination of a bilateral papilledema would seem to confirm this impression, in spite of a normal pulse, respiration and blood pressure. As is so often the case, we were unable to elicit any neurologic signs to suggest lateralization – the pupils were equal, all the deep reflexes were depressed and pathologic toe signs were present bilaterally. This uncertainty made it obligatory to explore both subdural spaces, with the disclosure of a bilateral subdural hematoma.

The frequent occurrence of bilateral lesions of this sort is higher than is commonly recognized, and in most cases, certainly in the presence of any doubt, burr holes should be made on both sides. It is, of course, a tragic oversight to miss a lesion on the one side. The practice of bilateral exploration in any reasonable doubt is further indicated by the unfortunate habit of such hematomas to provoke false localizing signs.

The ultimate outcome in this instance was disappointing, particularly in view of the patient's prompt recovery of consciousness. The surgeon hopes for, and expects, prompt restoration of the patient's faculties after evacuation of a subdural hematoma. This patient gave promise of full recovery, but in a week he developed a left hemiplegia which, in a patient of 69, was suspected of being a result of an intercurrent thrombosis of the right middle cerebral artery. Repeated right stellate blocks were unavailing and the patient was discharged to his home in a vegetative state.

PATHOLOGIC FINDINGS

DR. COURVILLE: An autopsy was done by one of the staff of the coroner's service on September 20, 1952. Pleural thickening at the apices of the lungs with edema and consolidation of the lungs was found at this time. Healed surgical incisions covered bilateral burr holes in the temporal regions.

The brain and enveloping dura (C.C. 672) were forwarded to the Cajal Laboratory for further study. The internal surface of the dura showed the typical golden-yellow color of an old subdural hemorrhage. Adherent to the dura on the right side and to the brain on the left was found the thickened capsules of empty subdural hematomas which covered the anterior portions of the dorsolateral surfaces of both cerebral hemispheres (figure 1A). These membranes were thick and tough and quite firmly adherent to the dura externally and a thickened and opaque arachnoid beneath. When cut across, this capsule was found to envelop a flattened cavity which contained a small amount of fluid. On its external lamina an irregular layer of soft, gray tissue was presumed to be granulation tissue.

The large blood vessels at the base were remarkably free from atheromatous change.

The cerebral cortex showed only a mild degree of cortical atrophy affecting both hemispheres to an equal degree.

In the right central region was found an irregular area of cortical softening measuring 4 by 5 cm., its long axis lying along the postcentral gyrus, apparently due to occlusion of one of the ascending branches of the right middle cerebral artery.

In the temporo-occipital region of both cerebral hemispheres, in the area of dis-

tribution of the posterior cerebral artery were found additional areas of softening (figure 1B). On the right, the more or less completely softened area involved chiefly the basilar surface and the inferior lip of the calcarine fissure, extending forward in a more irregular fashion to involve the fusiform gyrus as far forward as the incus. On the left, the softening affected almost exclusively the cuneus.

Repeated sections of the brain stem were made at right angles to its long axis. No well-defined defects were visible to the unaided eye, either in the basilar or the tegmental portion of the midbrain or upper pons. In the former, however, at the level of the red nucleus, small irregular patches of yellow discoloration were found in the substantia nigra and in the underlying cerebral peduncles.

The cerebrum was cut in a series of horizontal sections. The upper sections disclosed in more detail the area of cortical softening in the right postcentral area (figure 1B). It was found that the softening process had affected not only the superficial cortex but also that bordering the depths of the central sulcus (thus accounting for the contralateral hemiplegia). In the lowermost sections the centrum beneath the central area appeared a chalky white and was firm to the touch. The lateral ventricles were markedly enlarged, about equally right and left. The third ventricle was also a large space, communicating through a greatly dilated aqueduct into a relatively normal-sized fourth ventricle.

The softening in the occipital areas of the two hemispheres was limited to the cortex and the immediate subcortex with subtotal destruction of the visual area on both sides. The white matter of the hemispheres, the basal ganglia, the remaining cortex and the cerebellum all appeared to be structurally normal.

A section taken from the margin of the capsule of the hematoma demonstrated both the external and internal membrane. The external layer was remarkably thickened and hyalinized with interstitial collections of compound (figure 1C). In the inner portion of this layer a loose connective tissue stroma was found to contain collections of red cells, many newformed capillaries and sinusoids. Occasional perivascular collections of round cells were also seen. The inner membrane of the hematoma was still very thin, being made up of a layer of cells with a few hyalinized connective tissue fibrils.

The cortical sections showed a considerable degree of thickening of the leptomeninges, particularly of its fibrous elements (figure 1D). These fibers had also undergone hyaline change presenting a remarkable degree of thickening so that the intervening spaces were considerably reduced in size.

Examination of the sections taken from the margin of the softened cortex disclosed both laminar and subtotal necrosis so characteristic of ischemia (figures 1E and 1F). A reactive gliosis was found both in the subpial glial layer and below the degenerated layer of cortex, with considerable hyalinization of the individual cells. The degenerated area was occupied by numerous compound granular corpuscles. In the less severely damaged cortex, there was observed a proliferation of newformed blood vessels. Most of the nerve cells in this area had disappeared or showed effects of severe damage. Some of the meningeal and cortical vessels showed recanalization, which suggested an original occlusion by a thrombus. Scattered perivascular collections of lymphocytes were also seen.

The subcortical white matter was sometimes involved in the softening process. Otherwise that portion which

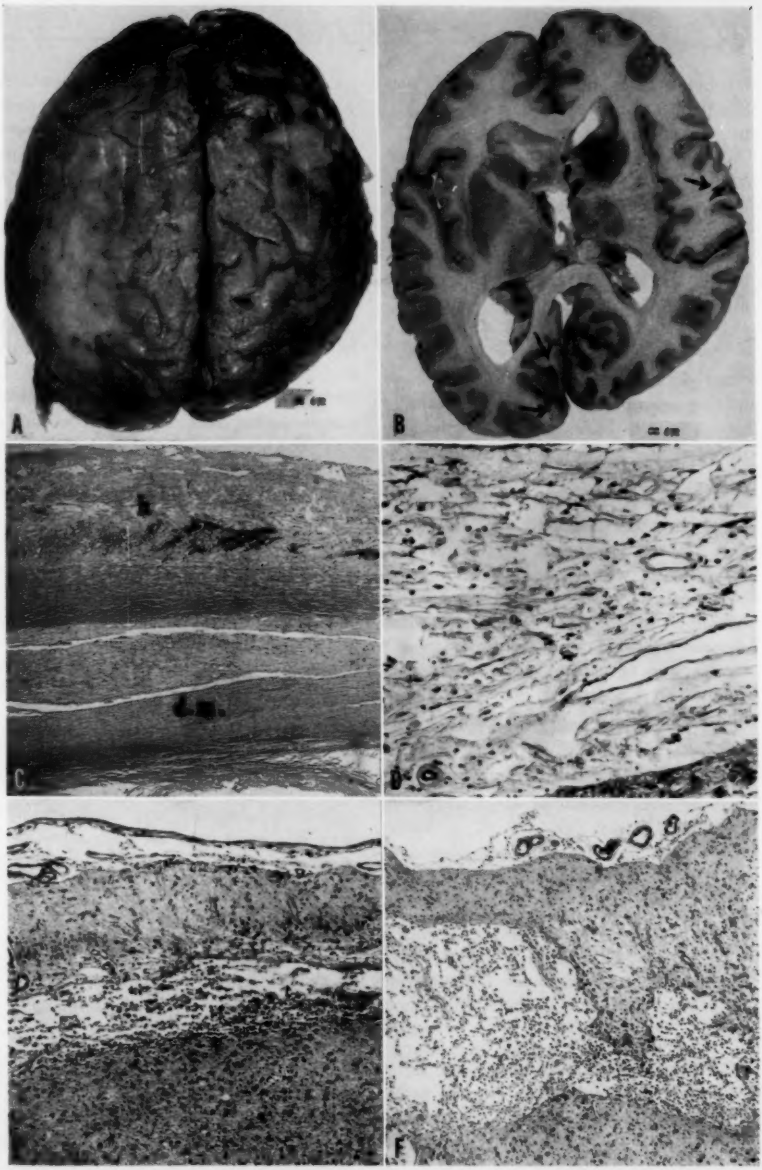

FIG. 1. Cerebral softening as a complication of chronic subdural hematoma. *A*. Residual capsule of subdural hematoma. *B*. Horizontal section of cerebral hemispheres showing softening of medial aspect of the left occipital lobe (the softening on the right does not show at this level) and in the right central area (arrows). Enlargement of the lateral ventricles is also evident. *C*. Low power photomicrograph showing dura mater (d. m.) and well organized external membrane of hematoma (h). The dark areas are collections of hematogenous pigment. *D*. Proliferation and hyalinization of fibrous elements of the arachnoid. *E*. and *F*. Laminar and irregular patchy necrosis of cortex adjacent to the areas of softening.

lay beneath the degenerated cortex was filled with vacuolar fluid spaces indicative of edema.

Sections taken from the margin of areas of softening in the white matter showed these areas to be quite sharply delimited. Within the confines of the area numerous macrophages were seen. In the surrounding area, clear vacuoles suggested the presence of edema.

DISCUSSION OF PATHOLOGY

DR. COURVILLE: We have in this case another example of the vascular complications of the brain which occasionally are consequent to acute extra- or subdural hemorrhage or chronic subdural hematoma. These complications have been recently described by Courville and Amyes.[1] In brief, in the chronic phase, with which we are here concerned, they consist of occasional focal softenings of the cortex and subcortex beneath the hematoma, at times by irregular foci of central softening of the compressed hemisphere, gross softening total or subtotal, of the cortex and subcortex of the basilar surface of the temporal lobe and the basilar and medial surface of the occipital lobe, and residual hemorrhagic cysts in the brain stem. As complications of acute traumatic dural hemorrhages, cerebral edema, rarely hemorrhages into the corpus callosum, the uncus and other regional structures, red softening of the cortex and subcortex in the distribution of the ipsilateral posterior cerebral artery and hemorrhages in the brain stem are often to be found at autopsy.

There are some important lessons to be learned from this tragic case. In the first place, the only adequate means of prevention of these crippling and ultimately lethal vascular complications is a prompt evacuation of blood clots from the extra- and subdural space or of encapsulated subdural hematomas. These lesions should invariably be considered as surgical emergencies! Delay invites disaster. This case also proves that complications may also occur after apparent recovery following evacuation of a hematoma, not from an intercurrent vascular lesion as was suspected but from characteristic complicatory lesions as their type and location so clearly show.

ANATOMICAL DIAGNOSIS: Multiple vascular lesions of the brain complicating bilateral subdural hematomas.

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Most of the writers on megrim and sick-headache have observed how frequently the malady makes its first appearance in childhood, and how seldom it commences after the age of thirty. Tissot particularly has drawn attention to the subject: he says that cases often begin at the age of seven and eight (period of second dentition), and even much earlier, and then are generally hereditary; while patients, who are not so predisposed, are more frequently attacked from the ages of thirteen or fourteen up to eighteen or twenty, and very few at all after the age of twenty-five. Romberg has also observed that the children of parents who have suffered from the malady are frequently attacked at an early age. Dr. Symonds found that about half of his cases of headache commenced in early life, and a very large proportion of the patients used the formula—"as long as they could remember."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CASE REPORT

Intramedullary Spinal Cord Metastases from Lung Carcinoma

Simulating Primary Cervical Cord Tumor

George C. Rasch, M.D., David Rosenbaum, M.D. and Robert F. Heimburger, M.D.

PRIMARY CARCINOMA of the lung metastasizes frequently to the brain but infrequently to other portions of the nervous system. The incidence of metastases to the brain varies with different reports. Beeler and Irey[1] found intracranial metastases in 21 of 35 cases with carcinoma of the lung. Fried[2] found 11.1 per cent metastases in 319 such cases. Hematogenous spread to the vertebral column is not uncommon, and the spinal cord and nerve roots may be compressed by epidural metastatic lesions.[3] However, metastases to the spinal cord itself are rare. The incidence cannot be stated accurately since examination of the spinal cord is omitted in many autopsies.

Cantor and Stein[4] recently reported a case presenting paraplegia resulting from intramedullary spinal cord metastasis from a bronchogenic carcinoma. They stated that only 13 verified cases of pure intramedullary metastasis could be found in reviewing the literature. In reporting a series of 100 cases of lung tumor with central nervous system metastases, King[5] found that when the spinal column was involved the metastases were never found in the substance of the cord. Wilson and Rupp[6] reported two cases of intramedullary spinal cord involvement by metastases; one from a tumor of the adrenal medulla and the other a case of Hodgkin's disease. In this same series the metastases from lung tumors compressed but did not involve the spinal cord. Craig[7] reported a case of lung tumor in which metastatic cells and necrosis were found in the thoracic portion of the spinal cord. Spencer[8] described a case of bronchiogenic carcinoma with a metastatic lesion in the lumbar spinal cord proven at autopsy.

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FIG. 1. Cervical myelogram demonstrating presence of intramedullary tumor centering at the third cervical vertebra.

CASE REPORT

A 45 year old white man entered the Indianapolis Veterans Administration Hospital on August 10, 1949, complaining of pain in his right arm. Symptoms began in March 1949 with development of a severe cough which caused pain in the neck radiating down the right arm. The pain was increased by coughing and straining with bowel movements. Frequent use of codeine was necessary. An orthopedic surgeon performed bilateral scalenotomy which did not help. The pain became worse and weakness was noted, first in the right arm and then in the right leg. Significant physical findings on admission were confined to the neurologic examination. Cranial nerves were intact and no papilledema was present. Deep tendon reflexes on the right side were hyperactive. A positive Hoffmann and a questionable Babinski reflex were noted on the right. Hypesthesia was present over the right chest, arm and leg. Position sense in all fingers and toes was impaired, especially on the right. There was weakness of all muscles of the right arm and to a lesser extent of the right leg. Coordination in the extremities was poor. The Romberg test was negative. Spinal fluid examination showed no cells and a total protein of 99.5 mg. per cent. Chest x-ray was reported as negative. Because of the hemiparesis, the ipsilateral hypesthesia and a lack of signs indicating nerve root involvement, an intracranial lesion was first suspected and a ventriculogram was performed. No abnormalities were present. The patient developed more pain and then weakness and sensory loss with a definite dermatome pattern in the left arm. A myelogram was done and a cervical intramedullary spinal cord tumor at the level of C_6 was demonstrated (figure 1). Laminectomy was performed on September 2, 1949, from C-2 to C-6. The cervical spinal cord was found to be enlarged with increased vascularity and distortion of the normal anatomic pattern. No incision was made into the cord as no area could be seen or felt which indicated that the tumor could be reached without causing further neurologic damage. Postoperative x-ray therapy was given to the cervical spinal cord region. About one month after operation the patient had hemoptysis of pure blood. A chest x-ray showed what was interpreted as a pulmonary infarct in the right lower lobe. In addition, the admission chest film was reviewed and a strand-like density seen in the right lower lobe which was felt to have been a healing infarct. The patient was given heparin. On October 8, 1949, he suddenly became confused and rapidly comatose. Temperature rose abruptly to 108° F. and generalized convulsive movements were noted. In spite of supportive therapy the patient expired in a few hours.

At autopsy a tumor occluding the right lower lobe bronchus was discovered. There were two infarcts in this lobe, one fairly recent and the other rather old. Microscopic examination of the lung tumor showed a highly malignant squamous cell carcinoma. Metastatic tumor was found in the adrenals, one of which weighed 700 gm. A small focus of tumor tissue was found in the left frontal lobe of the brain. Microscopically, this lesion was an undifferentiated tumor with much necrosis. The spinal cord was almost twice normal size from the second cervical segment to the upper thoracic area. The enlarged cord was soft with loss of normal appearance and color. The remainder of the spinal cord appeared grossly normal. The cervical vertebrae, epidural tissue and meninges were not involved by tumor tissue. Sections were taken from the

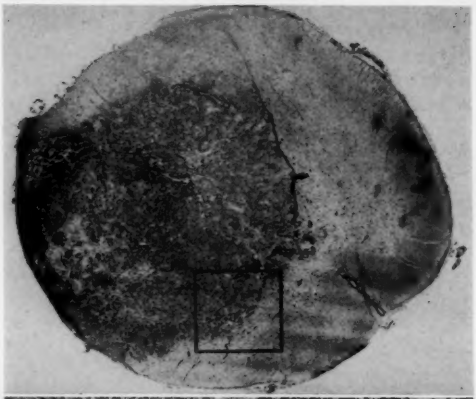

FIG. 2. Cross section mid cervical spinal cord with large metastatic intramedullary tumor.

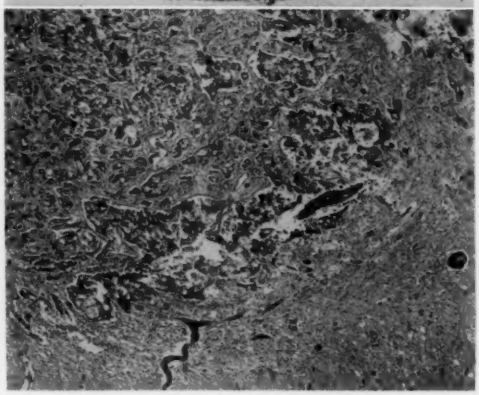

FIG. 3. Higher magnification of intramedullary tumor showing cellular detail.

spinal cord at intervals throughout its length. The cervical cord was found to be filled with tumor tissue. This was best shown by a section through the middle cerivcal area (figure 2). The neoplastic tissue was present in the form of a rounded mass within the cord substance, predominantly on the right side. The tumor cells were anaplastic with occasional resemblance to squamous epithelium (figure 3). No tumor was seen in sections through the lower cervical cord, but demyelinization and necrosis in areas corersponding to the location of the tumor were noted. Degeneration of axis cylinders was seen and many fat vacuoles were noted in sections along the cord, always located in the right anterior quadrant in the area corresponding to that occupied by the tumor in the cervical region. The area of degeneration became sharply localized in the lower thoracic and lumbar portions of the cord. Pathologic diagnosis was carcinoma of the right lower lobe bronchus with metastases to the cervical spinal cord, brain and adrenal glands.

DISCUSSION

Many cases[5,6,8,9,10] have been reported in which metastases from lung tumors produced clinical syndromes closely simulating primary central nervous system neoplasms. Often the metastatic nature of the disease was discovered only at autopsy. If an autopsy had not been

done in the present case the final diagnosis would have been primary intramedullary spinal cord tumor. The presenting complaint in this case of "root type" pain is common in cervical spinal cord tumors. Craig,[11] in reviewing a series of cervical spinal cord tumors, found that 76 per cent of the intramedullary tumors produced pain as the initial symptom, and 93 per cent of the entire group of 68 cases suffered "root type" pain at some time during the course of illness.

The route of spread of the lung tumor to the cervical spinal cord in this case is uncertain. Hematogenous spread from the lung via the heart to the general circulation and then to the spinal cord may have been the pathway. Ascent through the perineural lymphatics of cervical nerves to the subdural and subarachnoid spaces as suggested by Hassin[12] is a possible route of spread. Spread of tumor cells from a cerebral lesion via the cerebrospinal fluid to the spinal subarachnoid space may occur. It seems probable in the case presented here that the intramedullary lesion preceded the metastasis to the frontal lobe. The vertebral venous system may be the means of metastasis of the tumor to the spinal cord. In 1940 Batson[13] reported studies of the vertebral veins by means of radiopaque substances injected into human cadavers. He showed that the vertebral veins had a close association with the veins of the trunk and pelvis and also that the vertebral veins were connected with the dural sinuses. Batson[14] described the vertebral venous system as a plexus of valveless vessels carrying blood under low pressure, with direction of flow frequently arrested and reversed. He felt that the infrequency of intramedullary spinal cord metastatic lesions was due to the small size of the veins in the spinal cord as compared to the large vessels connecting the vertebral veins to the dural sinuses and brain.

Recently Anderson[15] has repeated Batson's work with injections in cadavers and in addition has studied living subjects with injections of Diodrast. He also concluded that the vertebral venous system was a continuous chain of vessels from the pelvis to the cranial venous sinuses, and that the circulation in the system is slow and subject to reversals in the direction of flow. Numerous connections were demonstrated between the vertebral system and the structures of the neck, chest and abdomen. From the work of Batson and Anderson, two possible pathways of spread utilizing the vertebral veins are suggested. The tumor cells may have passed from the lung through the azygos veins to the vertebral veins and then to the spinal cord. The spinal cord lesion may have arisen as a secondary metastasis from the adrenal lesion. Dissection studies by Anson[16] showed that the adrenal glands have venous connections by means of the vertebral system with numerous structures, including the spinal cord and meninges.

The course of this case would emphasize again the importance of careful physical examination and chest x-ray before any operation is carried out for suspected tumor of the central nervous system. Even though latent symptomatically, a primary lung tumor may be visible on the roentgenogram. This was true in the case presented although the lesion was not thought to be significant until the films were reviewed with the autopsy findings known.

SUMMARY

A case is reported of carcinoma of the bronchus with intramedullary metastasis to the cervical spinal cord. The metastatic nature of the spinal cord tumor was discovered only at autopsy. The routes by which the tumor cells might have spread from the right lower lobe bronchus to the cervical spinal cord are discussed.

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The causes of epilepsy may be divided into those which are remote, and those which are immediate. We must regard as the immediate or exciting cause that to which the first fit was apparently due. Of the two classes of causes, the former, the remote, is incomparably the more important. Most of the immediate causes of the first fit, although apparently influential in exciting it, are manifestly inadequate, alone, to account for its occurrence. Their effect is rendered possible by the antecedent predisposition. In a large number of cases no exciting cause can be ascertained; the first attack is then apparently the result of the predisposition only.

When one attack has occurred, whether in apparent consequence of an immediate excitant or not, others usually follow without any immediate traceable cause. The effect of a convulsion on the nerve centres is such as to render the occurrence of another more easy, to intensify the predisposition that already exists. Thus every fit may be said to be, in part, the result of those which have preceded it, the cause of those which follow it. The search for the causes of epilepsy must thus be chiefly an investigation into the conditions which precede the occurrence of the first fit.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CASE REPORT

Late Sequelae of Carotid Ligation

Charles E. Brackett, Jr., M.D.

The opinion has frequently been expressed in the literature that complications from carotid ligation in the neck are due to two causes: first, cerebral ischemia, with appearance of symptoms within six to eight hours after ligation; and, second, thrombosis, with appearance of symptoms after 12 hours. Many authors have implied that the majority of complications are caused by thrombosis, and that this holds particularly true when 12 to 24 hours have elapsed. That this may not be the case, however, has been emphasized by Schorstein's[1] case who, 48 hours after ligation, developed a slowly progressive hemiplegia and hemianesthesia which became complete after five days. At autopsy 13 days later, the carotid tree was found to be clean, and a typical anemic infarction of the hemisphere ipsilateral to the ligation was found. More recently it has again been pointed out that the majority of complications following ligation are due to anemic anoxia with infarction and not due to thrombosis.[2] The following case report is submitted to emphasize that (a) such a complication may occur as long as two and one-half days (57 hours) after ligation, and (b) with prompt treatment, immediate complete recovery may be achieved.

CASE REPORT

A 26 year old housewife had a two-week history of lacrimation, pain, ptosis, diplopia, and dilated pupil in the right eye. Examination revealed a blood pressure of 122/76, a pulse rate of 64, and a complete right third nerve palsy; the remainder of the examination was within normal limits. There was no evidence of subarachnoid bleeding, and all the pertinent laboratory studies were normal. Right carotid arteriography (figure 1) revealed a saccular aneurysm of the right posterior communicating artery close to its origin from the internal carotid. The posterior communicating artery was large and continuous with the posterior cerebral artery with the result that, in this case, the latter in effect received its blood supply from the internal carotid system. Compression of the contralateral (left) carotid artery resulted in excellent bilateral arterial visualization by way of the anterior communicating artery. Thus, there was evidence that, although the anterior communication was adequate, the posterior communication with the basilar artery might be small or absent.

The right carotid bifurcation was exposed in the neck and the internal carotid artery completely occluded by a 1 cm. tantalum band. This was well tolerated except for an immediate postoperative rise in blood pressure to 170/110 and an increase in

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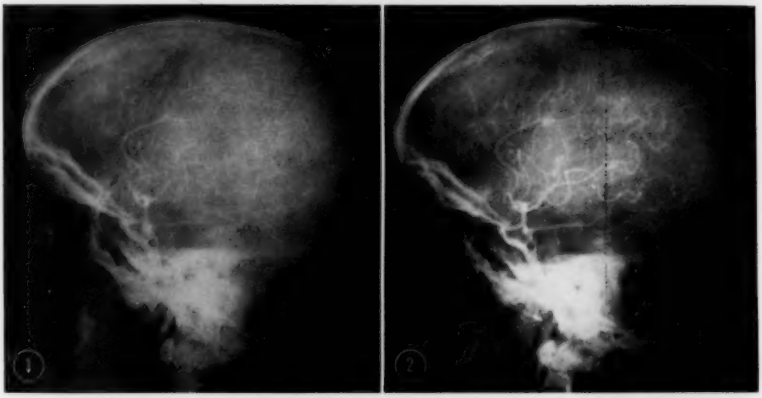

FIG. 1. Right carotid arteriogram demonstrating saccular aneurysm of posterior communicating artery at junction with internal carotid. Note filling of posterior cerebral via posterior communicating artery.

FIG. 2. Postoperative arteriogram to show diminished size of aneurysm and patent arterial tree.

pulse rate from 64 to 110/min. The patient was tested at five-minute intervals for the first 24 hours so that accurate observations were available. Four hours after ligation the patient became nauseated and complained of headache, while the blood pressure rose to 196/130, with a drop in the pulse rate to 60/min. Two hours later a slight left hyperreflexia and a slight weakness of the left grip were noted, but the third nerve palsy was less marked. Because of the possibility of impending cerebral infarction, a lumbar puncture was done. The cerebrospinal fluid pressure was normal (175 mm. of water) and the fluid clear. During the next 12 hours the blood pressure subsided to 140/100, while the slight degree of left-sided hyperreflexia and weakness disappeared.

The patient was then asymptomatic until 57 hours after ligation when, while talking to the nurse, she rapidly became drowsy and had difficulty elevating her left hip from the bed. She was found to have weakness of the left grip and thickening of speech. Within two minutes a complete left flaccid hemiplegia ensued and she complained of severe headache. A second lumbar puncture to rule out hemorrhage again revealed clear cerebrospinal fluid under normal pressure.

Utilizing the clip removal tray kept at the bedside, the neck was immediately reopened under local anesthesia. The internal carotid artery distal to the clip was collapsed to a diameter of 2 to 3 mm. The clip was removed exactly 20 minutes after the onset of the complication. The artery immediately filled out to its normal caliber and began to pulsate normally. Simultaneously, the patient, who had been conscious throughout this period, began to move her left arm and leg. Within ten minutes strength was nearly normal except for slight facial weakness, and within 30 minutes the headache was gone and the patient was entirely normal in all respects, except for a slight left hyperreflexia, which persisted for 36 hours, and the right third nerve palsy. She then experienced episodes of paroxysmal hypertension with headaches, during which she became emotionally disturbed for short periods. Sixteen days later, the neurologic examination was within normal limits and she had regained 75 per cent function of the right third nerve. Forty days after ligation the arteriogram was repeated and the aneurysmal sac found to be considerably smaller in size (figure 2). That this was not artefact from poor filling was ruled out by the excellent filling of the entire arterial tree. She was discharged 59 days after ligation, and was completely normal in all respects. The vital signs were normal and there was no evidence of the original third nerve palsy. When last seen,

eight months after ligation, she was asymptomatic in all respects, and again the neurologic examination was normal.

CONCLUSIONS

The preliminary episode of left-sided hyperreflexia and the sudden onset of symptoms, together with the findings at reoperation, the immediate recovery, and the postoperative arteriogram studies, support the thesis that this was a case of late-appearing anemic anoxia secondary to internal carotid artery ligation in the neck. The case is of importance because (1) it illustrates that this type of complication may appear unusually late, and (2) it again emphasizes that such complications should be actively investigated so that prompt treatment can be instituted to ensure an immediate complete recovery.

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We must regard, as the exciting cause of epilepsy, the condition or circumstance to which the first fit was apparently due. It may be again pointed out, to prevent misconception, that these exciting causes cannot be regarded as the essential causes of the disease, except in a very small number of cases. They would, in most instances, have been ineffective had not a predisposition existed, due to inheritance, or to causes which are at present beyond our recognition. To use a familiar but useful illustration, the exciting cause, as a rule, bears no more causal relation to the disease than does a spark to the explosion of the gunpowder on which it falls. The real cause of the explosion is the chemical tension of the constituents of the gunpowder, the existence of which is revealed by the action of the spark. The real cause of the disease is the morbid state of the nervous system, the existence of which is only revealed by the effect of the immediate excitant of the first fit. Nevertheless, since the occurrence of one fit undoubtedly facilitates the occurrence of others, we must regard the excitant of the first fit as, to some extent, the cause of the other fits, *i.e.*, of the whole developed disease. Without that cause, the disease might have remained forever latent.

The study of these causes presents peculiar difficulty. The statements made by patients have, of necessity, to be received with caution, and the facts to be carefully investigated. An occurrence so striking as a fit is naturally assumed to be due to some cause at least discoverable, and so is often attributed to a remote and improbable antecedent. Of 1,150 cases in which this point was noted, a reasonable cause for the first fit was given in 428, or 37 per cent, and in the remainder no probable cause could be ascertained. From this series the cases distinctly originating in dentition convulsions are excluded.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Neurology BOOK REVIEWS

Atlas of Tumor Pathology

Section X, Fascicles 35 and 37, Tumors of the Central Nervous System, by James W. Kernohan, M.D. and George P. Sayre, M.D.; Section II, Fascicle 6, Tumors of the Peripheral Nervous System, by Arthur Purdy Stout, M.D. Published by the Armed Forces Institute of Pathology, under the auspices of the Sub-Committee on Oncology, of the Committee on Pathology, of the National Research Council, Washington, D.C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D.C.; Prices 90 and 60 cents respectively.

These fascicles are portions of the larger *Atlas of Tumor Pathology*, covering the tumors of various regions of the body. Provided in loose-leaf form, to facilitate revision from time to time, they are nevertheless on excellent grade paper, and the nominal fee is far from an accurate guide to their worth.

The section "Tumors of the Central Nervous System" represents the mature consideration of a group which has, for a number of years, been concerned with large series of nervous system tumors. The senior author did much of the pioneer work in tumors of the spinal cord and of the ependymoma group. The classification employed departs in some respects from that familiar to many neurologists and neurosurgeons, but in a manner which is logically justified, statistically correlated, and designed to relate the gliomas to tumors in general.

After a brief introduction in which the section on cerebral edema is particularly valuable, the atlas continues with a concise and clear discussion of the tumor types. A particularly important feature of the arrangement is the inclusion of all the synonyms under each heading. This is followed by gross and microscopic illustrations of the types with appropriate legends opposite the plates—a very pleasant feature. It is obvious that considerable thought and care went into the selection of these excellent photographs to illustrate both the typical tumor and, to some extent, the variations more frequently seen. The gliomas are discussed first, followed by the tumors of mesodermal origin, then those arising as a result of developmental defects, and finally pinealomas, which were originally planned as a separate fascicle.

This volume will be welcomed not only by pathologists in smaller hospitals who will have to become increasingly concerned with these problems, but also by neurologists, neurosurgeons and neuropathologists who will find much food for thought in this clear and precise presentation. Needless to say, it should prove invaluable to those in training in neurologic fields, and particularly those contemplating board examinations.

The format and general plan of *Tumors of the Peripheral Nervous System* is similar to that of the *Central Nervous System* and of other fascicles already

released. It antedates the *Central Nervous System*, having been published in 1949.

Not everyone would agree that the classification, particularly of nerve sheath tumors, is necessarily the best, but one has to adopt some classification and certainly the author, who pioneered the work on tissue culture, is in a strong position to defend his view. Included among the excellent photomicrographs are some of explants from the author's tissue culture studies with Dr. Murray. Of particular interest to neurologists are the illustrations of the various clinical types of involvement in Von Recklinghausen's neurofibromatosis. The protean manifestations of this disease, as well as some of its histologic variations are emphasized.

These concise, clear, well illustrated and up-to-date volumes certainly merit a prominent place in the library of anyone in the field of neurologic sciences who has a serious interest in tumors of the nervous system. F. M. JR.

Anatomy of the Nervous System

Stephen W. Ranson, M.D., Ph.D. Ninth edition revised by Sam L. Clark, M.D. Ph.D. 1953. *Philadelphia: W. B. Saunders Company.* 581 *pages,* 434 *illustrations,* $8.50.

In the present revision by Professor Clark of this standard textbook there has been much desirable recasting of the material with no loss of the essential form and purpose of the original work. Readers accustomed to the earlier editions will feel quite at home in this one, so skillfully has the newer knowledge been grafted on to the old. The organization of the book has not been changed since the last revision. An introductory descriptive account of the gross anatomy of the human nervous system is followed by sections dealing with the microscopic structure and internal organization of its component parts. Throughout emphasis is placed upon anatomical interrelationships and functional significance of the structures. The final section comprises a set of well selected and well printed illustrations of sections through the brain in transverse, oblique, horizontal and parasagittal planes which serves as a small but very serviceable atlas.

The rapid accumulation of new information about the function of the nervous system has made necessary considerable expansion as well as revision of the text. Fortunately the author has succeeded in incorporating intelligible and accurate digests of the more pertinent newer developments without enlarging the volume unduly. Although the main attention is on fundamentals, the book is also an excellent exposition of applied neuroanatomy and for these reasons should keep its well established position as one of the best textbooks for medical students in its field. It also has great usefulness as a brief, convenient reference work for clinicians and others interested in the nervous system who are not themselves neuroanatomists. R. B. R.

Neurology

America's First National Neurologic Institute

*Pearce Bailey, M.D.**

When the American Academy of Neurology was founded in 1948 clinical neurology was reported to be at a low ebb.[1] Recoiling from recurrent splinter movements out of its own ranks into other medical specialties, a serious question arose as to whether or not neurology could ever develop into an enduring focal point for practice and research in diseases of the nervous system. Then the Academy suddenly took up its stride under the leadership of A. B. Baker, its first president. Immediately applying a concept of responsible presidential leadership, Baker and his colleagues formulated an action program aimed at a general consolidation of the field of neurology.

Since the early Academy activities in 1948, many significant events have developed within the domain of neurology, which testify that the Academy program is paying off in terms of tangible achievement. There is one particular development which, together with the circumstances crucial to its development, deserves special attention. Though this event is closely interwoven with the future of neurology, yet it has developed as the result of activating forces originating, for the most part, outside of neurology proper. It is the creation, in 1950, of America's first national neurologic institute—The National Institute of Neurological Diseases and Blindness of the Public Health Service at Bethesda, Maryland.

Presidential address to the fifth annual meeting of the American Academy of Neurology, Chicago, Illinois, April 10, 1953.

*Director, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare.

FACTORS LEADING TO CREATION OF THE NATIONAL INSTITUTE

The sudden creation of a national neurologic institute, following closely on the heels of an epoch during which neurology allegedly had reached a new low in its long struggle for recognition, appears somewhat paradoxical, to say the least. Let us glance backward a moment to see if this paradox can be explained.

Harvey Cushing,[2] at the close of World War I, was the first to petition for the establishment of a national neurologic institute for the investigation of combat injuries to the nervous system. Later during World War II, Foster Kennedy,[3] in a letter to President Roosevelt, expounded our ignorance of nervous disease and reemphasized Cushing's previous proposal. But these individualistic efforts, provocative as they were, lacked collective backing and quickly evanesced. It became obvious that neurologists by themselves were not adequately organized or understood by the public to bring into proper focus a national requirement. A new turn in paramedical philosophy was needed to provide a ground swell upon which the various elements of neurology could float in unity to press a common cause.

This badly needed ground swell was supplied by: first, a shift in accent from acute diseases to the more chronic and incurable ones; and second, the increase of support of medical research recently given by the Federal government.

In the period between 1937 and 1950 the death rate in the United States declined 15 per cent, largely because of discoveries of the sulfonamide drugs and antibiotics. This increase in the life span of Americans was accompanied by some shift in public interest from acute infectious diseases to long-term chronic diseases and disabilities of later life for which no cure is known. The principal disease categories highlighted in this new trend of interest were cancer, heart disease and the psychosocial aspects of mental health. However, important as these problems are to the nation's health, it was just a matter of time before this new trend would focus on diseases of the nervous system, for there are few groups of disorders which are concerned more with long-term disabilities or which carry a greater economic burden in their wake.

Running almost parallel with the new emphasis on chronic disease was a rising public demand for more medical research support from the Federal government. Thus, Federal support for medical research increased ten-fold from 1937 to 1952.[4] Part of this additional Federal outlay went to the National Institutes of Health, the principal research arm of the Public Health Service. The National Cancer Institute was founded in 1937, followed by the National Heart Institute in 1948, and the National Institute of Mental Health in 1949.

The spreading fingers of Federal support of medical research were bound to extend eventually to the neurologic field because of the serious public health problem which diseases of the nervous system present. As neurologists know, probably no other group of diseases cause such long-term crippling, and this

crippling is usually so severe as to cause profound psychological, social, and economic dislocation for the individual sufferer.

The first telling impact of increased public interest in chronic disease and Federal support of medical research was not on neurologists, but on the crippled neurologic patients, their relatives and friends. These patients saw for the first time a real opportunity to press for aid where their afflictions for centuries had been synonymous with social embarrassment, shame, and despair.

CREATION OF NEW VOLUNTARY HEALTH AGENCIES

There was a response to the plea of these socially segregated neurologic patients which was embodied in the formation of new voluntary health agencies dedicated to research and care of distinct neurologic disabilities. These include such groups as the National Multiple Sclerosis Society, United Cerebral Palsy, the Muscular Dystrophy Associations, and the Myasthenia Gravis Foundation.

The establishment of these new voluntary health agencies for neurologic disorders and the consolidation of older ones, such as the National Epilepsy League, supplied a wedge for opening a drive toward the creation of a national neurologic institute. They were the first to petition Congress to do something for the victims of neurologic disorders. But, as could be surmised, their first petitions were not aimed at the creation of a national research institute. Like clinical and academic neurology, the neurology of voluntary health groups had been splintered into distinct categories. Therefore, each voluntary group introduced its own bill to establish an independent institute for the particular disease which was their primary interest. At least five such bills were introduced.

The Surgeon General and the Congress, however, were quick to see the dangers of such splinter institutes of neurologic research as well as the administrative difficulties involved. Accordingly, they recommended that the splinters be joined to form a single institute for all neurologic diseases and for blindness. The voluntary health agencies endorsed the new plan with the result that America's first national neurologic institute was authorized in August 1950 by Public Law 692.[5] In a sense, a further splintering of neurology, which throughout its history had sapped the kernel of its growing strength, was averted on this occasion.

At the time of the creation of the institute in this manner, clinical neurology already had begun to show signs of its renaissance.[6] Experimental neurology likewise was on the march. Its development of new methodologies, new precision instruments, new potentialities in biochemistry and biophysics had opened up additional vistas for research in the nervous system which had aroused interest in universities, the National Research Council, the National Academy of Science, and the U. S. Public Health Service. The increased activity in clinical and experimental neurology gave final justification to the authorization of the institute and for a wide participation of all these groups in its program.

Probably some have wondered why the problem of blindness was attached to a neurologic institute. The explanation is that at the time the Congressional bills were presented for separate neurologic institutes, a bill also was introduced for the establishment of a national institute for blindness. At the time it appeared that a program in blindness research could be associated more harmoniously with a program of neurology than with any of the other programs at the National Institutes of Health.

This decision was wise. Although neurology and ophthalmology function as distinct specialties as a matter of clinical expediency, nevertheless, from a research standpoint their basic fabrics are closely knit. Diseases of the nervous system and of the eye have many factors in common. The eye is an outgrowth of the brain, and when a scientist examines the optic nerve and retina, he is actually looking at brain tissue. A broad program in neurologic research should include studies on the sensory endings of the nervous system, especially the eye and the ear. In its operations, therefore, the National Institute of Neurological Diseases and Blindness is really a national institute of neurologic and sensory disorders.

ORGANIZATION AND PRESENT STATUS OF THE NATIONAL INSTITUTE

The National Institute of Neurological Diseases and Blindness, in general, follows the same organizational pattern of the six other national research institutes of the Public Health Service: the national institutes for cancer, heart, mental health, microbiology, arthritis and metabolic diseases, and dental research. Like these other institutes, the responsibilities of the National Neurological Institute are broad. The provisions of Public Law 692 empower the institute, through the Surgeon General, to conduct research and training of its own in neurologic diseases and blindness; to support such research and training at universities and other institutions as relates to the cause, prevention, diagnosis and treatment of these disorders.

In spite of the depth of its mandate, the program of the National Neurological Institute is still barely off the ground. Its birth may have been overdue, but when it did happen the time was not propitious, being two months after the onset of the Korean War. This was the time that the nation began to tighten the purse strings of domestic programs to meet the needs of national defense. No appropriation was made available to the institute in 1950, and it was not activated even on a planning basis until 1951.

The largest part of the institute's present program is in research grants-in-aid and fellowships to universities and other institutions. The base of this program has almost doubled since 1951, but it still can support only a fraction of the grant applications currently being received, so great has been the recent surge of activity in this field.

An important segment of the institute's plans is its program for fundamental and clinical research at new Clinical Center in Bethesda. Here, there is a unique opportunity for a real cross-fertilization of laboratory investigations

and clinical studies. Some of you may think that this is the part of the institute's program which concerns you least. If so, I beg to disagree, for it has the potential to stimulate neurologic activity throughout the world; to add people to our present meager supply of clinical researchers; and to be a useful focal point for the integration of neurologic groups everywhere, and for the establishment of an effective liaison of neurologists with voluntary health agencies. Moreover, this clinical program will keep the general program in intimate touch with the life scene in neurology.

The most glaring deficiency in the institute's present program is its paucity of funds for the support of neurologic teaching grants to medical schools and stipends for training neurologists. We neurologists know that research and training are merely different points on the same assembly line. Both points must fire synchronously if a constructive research program is to endure. We neurologists also know that present facilities for the training of teachers are inadequate; and that there is a gap between the clinic and the laboratory, and between clinical neurology and other branches of medicine. Yet, in spite of these deficiencies, this part of our program is a hard commodity to sell. More professional and public enlightenment is badly needed.

FUTURE GROWTH POTENTIAL

So far we have considered the many factors leading to the creation of America's first national neurologic institute, its organization, and the present status of its program. Let us now speculate on the institute's potential for expansion. First of all, the basis of the institute's growth is not merely a matter of money. An adequate budget, of course, is essential for effective program performance, but this problem must be eventually resolved in the cold war of supply against demand.

There are more fundamental determinants of the future of the institute, which reside in the growth potential of neurology itself, and in the support given the institute, not only by neurologists but also by those too often forgotten people: the neurologic patients. I have referred to splinter movements of the past which have diluted neurology's central core and prevented it from growing into its own size. These splinter movements comprise deviations within the ranks of professional neurology to set up subspecialties under special interest groups; movements from other branches of medicine to carve out of neurology proper, certain diseases or technical advances for incorporation into their own programs; and movements by neurologic patients to set up autonomous activities through their surrogates, the voluntary health agencies.

This is not the place to discuss the desirability or justification of the various splinter movements, which, in many instances, appear to be amply justified and serving a useful purpose. This is the place, however, to emphasize my conviction that unless these divergent currents become a part of a central neurologic stream, the growth of neurology as a discipline will be impeded as will

the strength of the divergent currents due to their isolation from a natural parent stem.

In the same way, the growth of America's first national institute is dependent on the development and support of a strong central discipline which contains within its orbit all the special neurologic groups, and which is closely linked with all special categories of neurologic patients. It is only with this type of total support that a constructive national neurologic research program can be designed. Moreover, it is only in this way that the real need for a national neurologic institute can be spelled out and made intelligible to the public.

Has any progress been made to coalesce the splinters in neurology? I think so, definitely. The trail blazed by this Academy for a further consolidation of neurologists and neurological groups has already been described briefly. These activities are serving as strong levers to raise the program of the national institute off the ground. But the consolidating forces now at work to give a common objective to the various representatives of neurologic patients have not been mentioned as yet.

Some of you know of the recent organization of The National Committee for Research in Neurological Disorders, promulgated primarily by members of the American Academy of Neurology. This committee, under the chairmanship of a neurologist, is composed of representatives from seven voluntary health agencies concerned with neurologic disorders. Its purpose it to formulate and support a national program of training and research in neurology. This committee is already in action, and already has begun to bring its weight to bear in building an effective national neurologic program through teaching and research.

SUMMARY

In summary then, it would not seem to be an overstatement to say that the first piles already have been driven for the ultimate structure that America's first national institute is to assume. There is, of course, much heavy construction work ahead—construction that will require help from all quarters of neurologic interest.

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Sensory and Motor Loss After Non-Neural Injuries

43 Cases of Ascending Neuritis

Michael Kelly, M.D.

Out of 63 cases of interstitial neuritis studied a few years ago,[1] no precipitating cause could be found in 17, while 16 followed systemic disease and 30 followed disease or injury to nearby tissues. In many of the last group the damage did not involve a nerve trunk; the spreading motor and sensory signs were explained as reflex effects from damaged tissues.

This phenomenon has been called ascending neuritis. It is common in war, but less commonly reported in peacetime when the occasional case is often overlooked because it is hard to explain by orthodox neurology. But we know that every injury of somatic tissues causes a reaction in the central nervous system; ascending neuritis means only that this reaction has been intensified.

HISTORY OF ASCENDING NEURITIS

Robert Whytt[6] wrote in 1765 about sympathetic paralysis, and Wardrop[7] in 1817 reported a case of widespread sensory disturbances which followed a prick of a finger. Many later writers have seen the disturbances follow injuries to finger or hand,[8–20] wrist or forearm,[2,3,19,21,22] upper arm,[23,24] lower limb,[25–30] and trunk.[4] Many of the great neurologists of last century[31–37] thought that the nerve terminals were infected in the wounds and that the inflammation spread up the nerve sheath, but nobody could produce an ascending infection of nerves. Walshe[25] pointed out that the skin did not have to be punctured, and therefore infection could not be the cause. Babinski and Froment[38] and Dejerine[13] suggested that the motor and sensory signs were reflex. Babinski and Froment,[38] Leriche[39] and Livingston[40] argued that the diagnosis of hysteria, advocated by Hurst,[41] was unfair to the patients. Livingston[40] has clearly shown us the reality of this disorder; and Barré,[2,14,17,20,21,24,30] with other French writers, [3,15,16,18,19] has lately made it peculiarly his own.

Many writers have been unable to explain these nerve lesions; the temptation is to look for pressure on nerves. Thus pressure from a sling was blamed for spinal accessory paralysis which followed fracture of the opposite hu-

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merus.[23] Other mechanisms which have been suggested are: pressure on the dorsal interosseous nerve by supposed deep bursae in the forearm;[22] by adhesive plaster when a peroneal nerve lesion followed an intravenous infusion into the lower leg;[26] by an otherwise undisclosed "pelvic tumor" when femoral neuritis followed a blow on the tibia;[27] by a single muscular contraction at the time of the injury;[28] by an invisible ganglion of the wrist when ulnar palsy followed a blow on the hand.[42] In case 42 of this series the diagnosis of compression neuritis of the peroneal nerve did not explain the anesthesia of the sole.

An analysis of 43 instances of motor or sensory loss which followed minor damage to somatic tissues is presented in table 1. Only a few cases can be recorded in detail.

CASE REPORTS

Case 2.—A young man sprained his thumb playing football; the basal joint swelled and was painful afterwards. Two weeks later he complained of numbness of the thumb and forefinger. Examination revealed a swollen and tender metacarpophalangeal joint, and anesthesia of the thumb and forefinger extending proximally to the wrist joint on both aspects (figure 1). There was no paresis of muscles; no later history is known.

Case 12.—After a fracture of the lower end of the radius, the whole of the arm became weak, painful and numb, and the numbness extended to the chest. Seven months after the injury there was a deformity of the wrist, due to rotation of the lower fragment. Cutaneous sensation was absent all over the arm and the same side of the chest, up to the ear and down to the costal margin (figure 2), and deep pain sensation was absent over most of the same area. There was wasting and weakness of the muscles of the forearm, and pronounced weakness of the muscles of the upper arm and the shoulder-girdle. The patient was awaiting discharge from the army with a diagnosis of hysteria.

Case 15.—A small wound in the center of the palmar aspect of the forearm was dressed with an ointment which caused blistering of the surrounding skin. It healed normally, but three weeks later the patient awoke with mild aching pain and weakness of the forearm. The healed wound was surrounded by a small area of darkly-pigmented skin. There was a severe dorsal interosseous lesion, combined with paralysis of the flexor carpi ulnaris. The backs only of all five digits were insensitive to touch and pain (figure 3). Recovery commenced immediately, and was complete within six weeks.

Case 34.—A heavy fall on the buttocks was followed by severe coccydynia; there was no fracture or dislocation and a few wounds over the sacrum healed soon. The pain spread to the right buttock and thigh; the patient walked with a limp and he could not sit. Two weeks afterwards he felt numbness on the outer aspect of the leg; this later extended from the great trochanter to the toes. On examination after five months there was extreme tenderness of the coccyx and the attachment of the right gluteal muscles to the sacrum. The hamstring muscles were resistant. The skin over the coccyx was normally sensitive; but the outer half of the whole surface of the right leg was hypoesthetic, and anesthetic below the knee (figure 4). The deep tissues also were anesthetic; the outer toes could be crushed, the lateral malleolus could be struck heavily without pain, and the lateral popliteal nerve at the head of the fibula was insensitive to pressure.

Case 37.—A soldier sprained his right knee, which became distended with fluid. It was slow to recover and after two months he complained of numbness on the outer side of the thigh. Examination revealed extreme wasting of the quadriceps femoris, and anesthesia throughout the distribution of the lateral cutaneous nerve of the thigh (figure 5). The later history is not known.

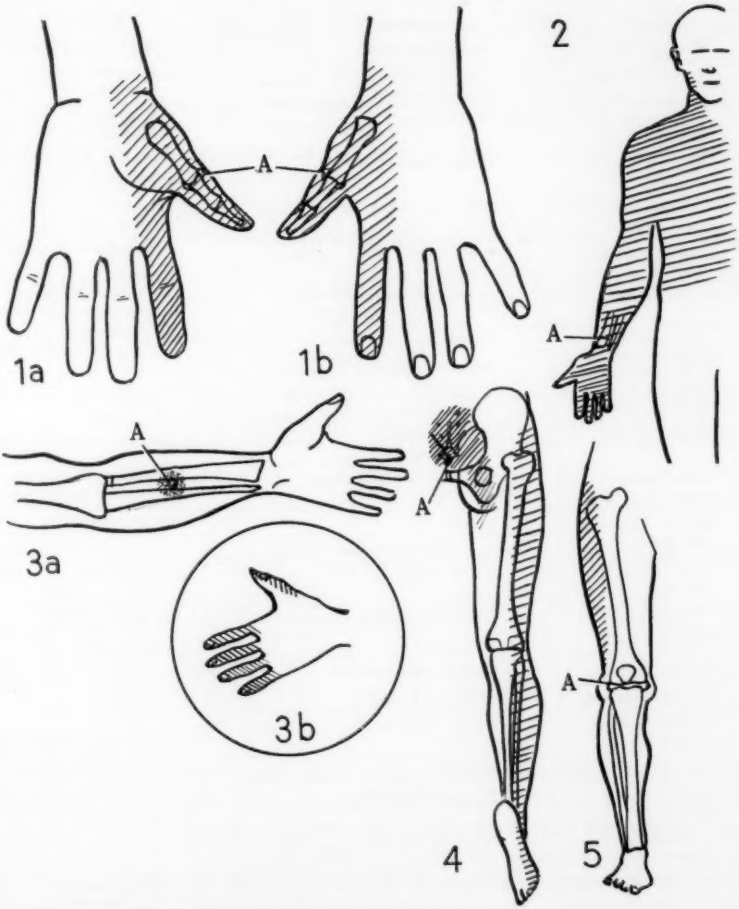

FIG. 1. Case 2. (a) Palmar view of hand. (b) Dorsal view. A = damaged metacarpophalangeal joint. Hatching = area of sensory loss. FIG. 2. Case 12. A = fracture of distal end of radius. Hatching = area of sensory loss. FIG. 3. Case 15. (a) Volar view of forearm and hand. A = small wound. Stipple = pigmented skin around wound. (b) = dorsal view of hand. Hatching = area of sensory loss. FIG. 4. Case 34. A = site of blow. Oblique hatching = tenderness of sacrum and right gluteal muscles. Horizontal hatching = area of sensory loss. FIG. 5. Case 37. A = traumatic synovitis of knee. Hatching = area of sensory loss.

TABLE 1

Case No.	*Injury*	*Nerves affected*	*Type*	*Remarks*
1.	Blow on wrist	Dorsal interosseous	M	Recovery in 2 months
2.	Sprained thumb	Glove to wrist: median and radial	S	More than 4 months duration
3.	Squeezed thenar eminence	Thenar muscles	M	More than 7 months duration
4.	Squeezed hand	Ulnar in hand	S > M	6 weeks interval before onset. Recovery
5.	Squeezed hand	Ulnar and medial cutaneous	S C	3 months interval before onset
6.	Wound of thenar eminence	Median up to wrist	S	Recovery in 2 months
7.	Colles' fracture	Dorsal cutaneous of forearm	S	6 weeks interval; recovery in 6 weeks
8.	Fall on hand	Partial radial and ulnar	S	recovery in 2 weeks
9.	Palmar cellulitis: incised	Partial median palmar	S	
10.	Wrenched wrist	Partial median to wrist	M = S	
11.	Wrenched wrist	Glove to wrist: median and radial	S	
12.	Colles' fracture: mal-union	Arm and chest wall. Glove	S > M	More than 9 months duration. Pain severe
13.	Fractured radius and ulna	Radial	S	
14.	Fractured radius and ulna	Partial median and ulnar	M = S	Median explored–normal
15.	Skin wound of forearm	Radial and ulnar	M = S	3 months interval before onset; recovery in 2 weeks
16.	G.S.W. forearm	Median and ulnar	S > M	
17.	Wound of forearm	Median and ulnar	M = S	
18.	Scratched papules on forearm	Glove: whole arm	S > M	
19.	Blow on back of elbow	Median	S	Recovery in 2 months
20.	Blow on lateral epicondyle	Glove: whole arm	S C > M	Pain severe; recovery in 8 months
21.	Osteoarthritis of elbow	Glove: 3/4 of arm	S C	
22.	Osteoarthritis of elbow	Median and ulnar	M = S	Partial recovery in 8 months
23.	Old wound upper arm	Skin 4" around	S	Duration 15 years
24.	Sprain right shoulder	L. plexus	M	Partial recovery in 6 months
25.	Sprain of shoulder	Suprascapular	M C	No recovery
26.	Typhoid vaccine (arm)	R. sciatic and femoral	S C > M	Partial recovery 2½ years. Pain severe
27.	Toxoid injection (arm)	Radial and patchy hyperalgesia	S > M	Recovery in 3 months
28.	Antitetanic serum (? buttock)	Lat. cutaneous of thigh	S	

TABLE 1—(continued)

Case No.	*Injury*	*Nerves affected*	*Type*	*Remarks*
29.	Myocrisin injection lat. thigh (rheumatoid arthritis)	Sciatic	S	Duration 8 days. Pain severe
30.	G.S.W. chest	Suprascapular	M C	No recovery 1 year
31.	Herniotomy	Legs, left arm	S = M	Severe widespread pains: neurotomy
32.	Appendix: re-exploration after 7 days	L. sciatic	S	No recovery 2½ years
33.	Excision of rectal polyp	Sciatic	S	
34.	Contusion of coccyx: coccydynia	Peroneal and lat. cutaneous of thigh	S C	More than 5 months duration
35.	Lipomata on thigh	Lat. cutaneous of thigh	S	Partial recovery 1 year
36.	Supracondylar fracture of femur	Lat. cutaneous of thigh	S C	
37.	Sprain of knee: synovitis	Lat. cutaneous of thigh and wasted quadriceps	S C	2 month interval before onset
38.	Sprain of knee: synovitis	Cuff anesthesia 4″ above and 4″ below knee	S C	Pain in knee severe
39.	Monarticular arthritis of knee after pneumonia	Stocking anesthesia below mid-thigh	S > M	Pain in knee severe
40.	Manipulation knee: rheumatoid arthritis	Sciatic	S	Recovery in 3 months
41.	Blow on calf	Lateral cutaneous of calf	S C	No recovery 3 years
42.	Fractured metatarsal: plaster	Peroneal and anesthesia of sole	S > M	
43.	Acute otitis media	Surrounding anesthesia for 2″	S C	Pain severe. Recovery 3 days

Key to type. M = motor. S = sensory. C = complete.

CLINICAL FEATURES

The injuries were mostly mild, though there were some severe sprains (cases 37, 38), wounds (cases 16, 30) and fractures of large bones (cases 12, 14, 36). In 12 of the 43 cases the hand or the wrist was injured, and in 16 other cases parts of the upper limb were injured. The paralysis usually appeared soon after the injury; in cases 4, 5, 15, and 37 it was delayed a few weeks. In some published cases it has been delayed for months or even years.[2] The skin was broken or punctured in only 15 (wounds, operations, injections); this shows that infection cannot be the cause.

The causative injury is often followed by disproportionately severe pain, often with a numbing quality. But in cases 1, 7 and 15 there was very little pain. The lesion is usually painful even when there is no loss of cutaneous sensation (cases 24, 25, 30); the pain is in the deep tissues. Non-traumatic painful disorders may cause persistent or transient loss of sensation in adjacent skin (cases 35, 39, 43).

Sensory or motor paresis may be complete or incomplete; sensory effects are more common and spread more widely than motor effects, and the deep tissues may be insensitive (case 34). Occasionally paresis may occur without loss of sensation (cases 1, 3, 24, 25, 30).[3] The motor effects vary from case to case: a muscle may be grossly wasted without paralysis (case 37), or it may be paralyzed with very little wasting (case 20).

Sometimes loss is limited to the field of a nearby nerve-trunk (cases 1, 7, 36, 41, etc.); more commonly it spreads into portion of the fields of more than one nerve (cases 2, 15, 24, 42, etc.). Sometimes a well-defined patch not related to any nerve fields develops around the lesion (cases 23, 38, 43). Usually the effects do not spread far and often they are transient (cases 8, 15, 29, 40, 43); less common is the extreme spread, even to other limbs, which is more likely to appear in the literature (cases 12, 26, 31).

Sometimes the spread is not spatially continuous, but the effects develop first at a distance from the lesion, even in another limb or a different part of the body (cases 24, 26, 40). This has been differentiated from ascending neuritis and called reflex paralysis,[4] but the pathologic process is the same.

Postinjection Palsies. In cases 26, 27, 28 and 29 neuritis followed hypodermic or intramuscular injections which did not damage nerve trunks. In cases 27 and 29 the fields of local nerves were involved; but in case 26 an intractable sciatic and femoral palsy followed an injection of vaccine into the arm. Palsies which follow prophylactic injections are usually preceded by evidence of a general systemic disturbance (urticaria; general muscular pains).[5]

COURSE

Course. Most of the mild cases recover early, or the residual disability is not great if they do not recover completely. In the severe cases a painful disability may persist for years, and an erroneous diagnosis of hysteria or malingering may add to the patient's distress (as in cases 12, 26, 31, 33, 39). Operations to relieve supposed pressure on nerves seldom bring relief (case 31); section of nerves often intensifies the pathologic process in the cord.[43]

PATHOLOGY

In two cases of ascending neuritis the cord has been examined at autopsy.

Dejerine[13] reported that a patient with tabes dorsalis pricked her left thumb. Pain spread up the hand and forearm, with atrophy of the skin and some wasting of muscle. After the patient died of tuberculosis, degeneration was seen in the median and (less) in the ulnar and radial nerves. The sixth and seventh cervical posterior roots had shrunk and their ganglia had lost many cells. In both sides of the cord in this region the posterior horns had atrophied; the rest of the cord showed no such changes.

Dereymaeker's[3] patient, whose paralysis was motor, was struck on the left elbow. Two weeks later the arm became paralyzed, and pain was felt between the scapula. The legs became weak and then the right arm. After seven months he died from infarction of the lung, and examination of the spinal cord showed widespread atrophy of anterior horn cells.

Chromatolysis. Marinesco[44] suggested that ascending neuritis was due to chromatolysis—a lesion of the neuronal bodies in response to damage to nerve

fibers. This is the customary response to injury of a large nerve trunk.[43] When somatic tissues are diseased or damaged a large number of smaller nerve fibrils are injured, with changes in the ganglion cells. If an animal is killed a few days after extraction of a tooth, changes will be found in cells in the trigeminal ganglion.[45,46] At human autopsies, the posterior root ganglia of the corresponding segments have shown chromatolysis in diseases of the skin,[47,48] bedsores,[49] chronic infective arthritis,[49] rheumatoid arthritis,[50] frozen shoulder which followed myocardial infarction,[51] and many other diseases.[52] In rheumatoid arthritis many anterior horn cells degenerated.[50,53]

Other things being equal, chromatolysis is inversely proportional to the distance of the lesion from the cell, and directly proportional to the intensity of the damage to the axon.[43,44] But other factors are not known, and occasionally an intense reaction is set up by minor damage at a great distance from the patent cell.

Transneuronal degeneration. After an experimental nerve injury the neuronal disturbances usually extend beyond the cells originally involved.[54–64] Even when no neurologic abnormalities have been detected before death, damage to large groups of cells can be seen on microscopic examination of the cord. Motor reflexes are disordered during chromatolysis of motor neurones.[65–68] The spread of sensory effects, due in part to chromatolysis of individual neurones, whose axons divide and send branches into different nerves,[43] is chiefly due to transneuronal spread. When the effects of injury to a mixed nerve are almost wholly sensory or almost wholly motor, this is due to disproportionate trans-synaptic spread through a whole system of neurones.

Even the mildest injury causes chromatolysis of neurones; in rare cases this reaction is greatly intensified and spreads to other neurones. Sensory effects outweigh motor effects because sensory fibers branch freely in and beneath the skin,[69] and in deep fascia and synovial membrane.[70,71] Thus most wounds, blows and sprains directly damage only sensory fibers, and even with equal damage to a mixed nerve trunk, chromatolysis is more intense in sensory than in motor cells.[43,44,57]

Normally, most of the neurones recover from chromatolysis within a few weeks. Therefore we should not be surprised to find that the manifestations of ascending neuritis are often transient. When they are severe and persistent, new unknown factors have taken charge which accelerate the spread and intensify the neuronal changes. By this time the process has become independent of the precipitating injury and is a self-perpetuating disorder of the cord.

SUMMARY

1. Ascending neuritis is a spreading sensory or motor disturbance, with pain, which appears after a minor injury to non-neural tissues.

2. It is the effect of chromatolysis of neurones, which is a normal reaction to injury of peripheral tissues.

3. In ascending neuritis this reaction is intensified and transmitted from cell to cell, so that large numbers of neurones are disturbed and may perish.

4. In a series of 43 cases, loss of cutaneous sensation was more common than motor loss; the hand or the forearm was injured in more than half of the cases.

5. The skin was punctured in only 15 cases; infection therefore cannot be the cause.

6. Ascending neuritis is often diagnosed erroneously as hysteria or malingering.

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Ammonium Chloride as an Adjuvant to Anticonvulsant Medication in Epilepsy

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For one and one half years ammonium chloride has been given to a selected group of epileptic patients in addition to anticonvulsant drugs. Since a preliminary report,[1] investigations have been extended. The ammonium chloride was given to add a dehydrating and acidifying agent to anticonvulsant drugs. It has long been established that dehydration, as well as the tendency toward acidity, decreases the occurrence of epileptic convulsions. Fay[2] used dehydration for the treatment of epileptic patients and restricted the fluid intake to 300 to 500 cc. in each 24 hour period. Wilder,[3] concluding that ketosis was the factor responsible for the beneficial effect of fasting on epilepsy, started to experiment with diets high in fat and low in carbohydrates. For a time this ketogenic diet was generally used for the management of epileptic children, and patients with cryptogenic as well as symptomatic epilepsy improved. However, both the dehydrating and ketogenic diets are very unpleasant and difficult, if not impossible, to carry out over long periods.

Ammonium chloride appeared to be a comparatively non-toxic drug which would combine the dehydrating and acidifying effect. Ammonium chloride dehydrates by the elimination of water through its diuretic action. If it is ingested, ammonium is liberated and tends to produce acidemia. It has the additional advantage of being cheap and available in enteric-coated tablets.

The procedure has been standardized, as follows:

1. After admission the patient stays on his previous medication and the epileptic pattern is studied.
2. An electroencephalogram is made and Lambda studies are done to estimate the ionized calcium in the blood.
3. Ammonium chloride is given in addition to previous medication. In the beginning we gave only 4 gm. of ammonium chloride, but now a dosage from 6 up to 10 gm. is used, given in divided doses four times a day.
4. The electroencephalogram and Lambda studies are repeated.

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In 1928 Lennox and Cobb[4] investigated the question of whether acidosis produced by means other than by accumulation of carbon dioxide and by ketosis is effective in reducing the number of seizures. To produce an "inorganic acidosis" they gave patients who were not under anticonvulsant drugs calcium chloride, ammonium chloride, magnesium sulfate and ammonium nitrate alternately, and observed the changes in the seizure pattern. Electroencephalographic studies were not available at that time. They came to the conclusion that acid-forming salts may in some patients cause a reduction in the number and severity of seizures. Continued use of acid forming salts, calcium chloride and ammonium chloride, however, may be followed by a great increase in the number of seizures, due possibly to the accumulation of chloride in the tissues.

Examination of their graphs indicated that ammonium chloride was invariably beneficial, a reduction from 90 to six seizures a day being obtained in one case, from 12 to two in the other. The anticonvulsant effect of ammonium chloride and its practical utility were probably ignored because it was considered only as one of a group of acidifying agents, some of which appeared to be without value. This is obviously the reason that up to recently ammonium chloride had not been added to the therapeutic armamentarium in epilepsy.

The 27 cases herein presented had suffered for many years from epileptic seizures which could not be adequately controlled with the usual drugs. Such a selection was necessary in order to judge the effect of an additional drug. Of course, evaluation was greatly facilitated by the objective tracings of the electroencephalogram.

Nineteen of the patients were over 18 years of age, in seven of whom seizures had persisted from 20 to 38 years. Eight were under 18 years of age. In five patients the seizures were probably post-traumatic, in others cryptogenic. In most cases there was a combination of grand and petit mal, with the occasional addition of psychomotor equivalents. Three patients had only psychomotor seizures.

It was necessary to separate changes in the clinical states and the electroencephalographic pattern following ammonium chloride therapy. The correlation between clinical and electroencephalographic improvement was not complete. For example, the electroencephalogram might become normal while occasional seizures still occurred. Also, the reverse was true, in that seizures might be abolished while the electroencephalogram still showed slight abnormalities. In a number of patients marked improvement in the mental picture was observed with the decrease in seizures. In others, especially children, this was not always the case.

The enteric-coated ammonium chloride tablets did not produce untoward side effects in any of the patients. In two children and one adult, who had been on the medication for a long period, x-rays of the wrists and pelvis were carried out but failed to show signs of calcium depletion. Ammonium chloride is one of the most widely used saline expectorants, given in doses of

TABLE 1

27 CASES OF EPILEPSY AFTER NH_4CL ADDED TO ANTICONVULSIVE THERAPY

Clinical Status		*Electroencephalogram*	
8	100% improvement	8	100% improvement
13	60 to 90% improvement	7	60 to 80% improvement
3	40 to 60% improvement	6	30 to 50% improvement
3	no improvement	5	no improvement
		1	normal before NH_4Cl

0.3 gm. every two hours. One would expect that the comparatively large doses of ammonium chloride would cause some difficulty with increased bronchial secretions. It is interesting to note that this difficulty is avoided by the use of enteric-coated tablets. The experimental observations of Perry and Boyd[6] demonstrated that ammonium chloride increases the respiratory tract fluid through its reflex action from the stomach. When the branches of the vagus supplying the stomach were cut, ammonium chloride introduced into the stomach was not effective.

Calcium lactate, .65 gm. three times a day, was given with the ammonium chloride in six cases. The total blood calcium values are not abnormal in epilepsy and it has been shown that calcium alone does not affect the seizures favorably. However, it was considered that the beneficial effect of ammonium chloride might be the result of an increase in ionized calcium in the blood, and that this might be enhanced by adding calcium to the diet. In fact, in two cases, a child and a woman, a marked response was observed when calcium was added to the ammonium chloride. Ionized calcium is extremely difficult to measure – the usual method being a physiological assay using a perfused frog's heart. In order to evaluate the effect of ammonium chloride on ionized calcium, determinations of the factor Lambda of excitation were carried out. It has been shown that this factor varies with ionized calcium.[7] A clinical estimate of this factor was attained by determining the ratio of threshold of muscular excitability at frequencies of 10 per minute and 10 per second, using a sinusoidal current. These determinations were carried out in ten patients and showed an increase in eight and a decrease in two. As yet these determinations do not permit any definite conclusions; they are reported as entirely preliminary but worthy of further study.

The following case illustrates the gradual clinical and electroencephalographic improvement following addition of ammonium chloride with simultaneous reduction of previous anticonvulsant medication.

A 21 year old Indian boy had suffered from petit mal seizures since the age of eight. At the age of 17 he suffered his first grand mal attack. He was placed on phenobarbital and at first the convulsions came at intervals of about four months. The attacks then became increasingly frequent, and in January 1950 he developed status epilepticus and was hospitalized at the Wisconsin General Hospital. During his stay in the hospital grand mal seizures disappeared after he was put on a treatment regimen of 0.1 gm. Dilantin four times a day, and 0.1 gm. phenobarbital on retiring. However, the petit mal seizures

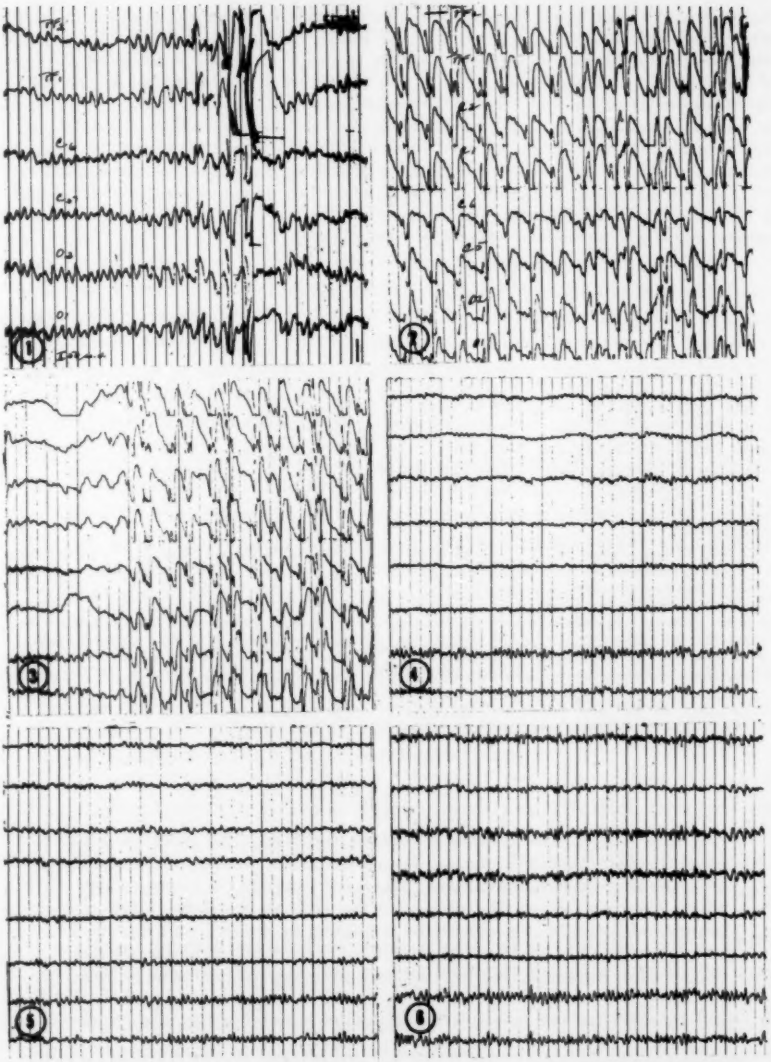

FIG. 1. January 24, 1950: Electroencephalogram three days following status epilepticus. FIG. 2. September 6, 1951: Electroencephalogram after patient had been on Dilantin, Mesantoin, phenobarbital and Tridione in various combinations. FIG. 3. September 26, 1951: Ammonium chloride 8 gm. daily, added to Dilantin 0.3 gm. and phenobarbital 0.3 gm. daily. FIG. 4. October 2, 1951: Current medication phenobarbital 0.3 gm. and ammonium chloride 10 gm. daily. FIG. 5. October 24, 1951: Electroencephalogram three weeks later, during which time the patient had four "staring" spells. FIG. 6. March 21, 1952: No seizures since October 1951.

occurred about twice daily. Improvement continued for a while, but later the spells of staring increased to three or four per day, and the patient developed frequent seizures in which he fell to the floor without a convulsion, but with occasional incontinence. In one of these seizures he fractured his jaw. He was readmitted to the hospital in August 1951, and was given large doses of Dilantin, Mesantoin, phenobarbital and Tridione, alone and in various combinations, with no relief. Ammonium chloride was added to the Dilantin and phenobarbital. Finally the seizures were abolished on a regimen of 0.3 gm. phenobarbital and 10 gm. ammonium chloride daily. Following discharge from the hospital, he had four convulsions up to October 24, 1951. Since then he has had no convulsions and is able to work. On March 21, 1952, his medication was reduced to 0.26 gm. phenobarbital and 8 gm. ammonium chloride per day.

Treatment of the epileptic patient requires careful evaluation of his personality and reactions to physical as well as psychological factors. Every case requires individual and prolonged study for an adequate choice of drug combinations. Ammonium chloride as an adjuvant to anticonvulsant therapy has not only brought about marked improvement in severe cases of epilepsy which were refractory to other drugs, but has made it possible to reduce these drugs in a number of cases. This is important since anticonvulsants may produce toxic manifestations and may affect the mental faculties of the epileptic. A number of patients have been rehabilitated and have returned to work.

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A rare but curious condition sometimes attends the onset of a fit which begins unilaterally; it may be termed the alternation of the aura. In some right-sided convulsions, from left meningeal hæmmorrhage, which I once watched, the rotation of the head to the right, which accompanied the fit, was preceded by a rotation to the left, and this itself was preceded by a slight initial rotation to the right — a double alternation. I have obtained very few indications of this phenomenon in idiopathic epilepsy. In one case a left-sided fit was preceded by shaking and trembling of the limbs of the right side; in another case the attacks began with a sensation in some left cranial nerve, followed by a sensation around the right wrist.

The great majority of fits which begin unilaterally are purely epileptic. Of 76 in which the character of the fit could be ascertained, only 9 (or 12 per cent) presented hysteroid convulsion.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Myelography by Means of I^{131}

The Myeloscintigram

Franz K. Bauer, M.D. and Eric T. Yuhl, M.D.

It is the purpose of this preliminary report to describe a new technique of myelography which employs radioactive tracer techniques, and to discuss its advantages over the conventional technique of contrast myelography. The introduction of contrast substance, such as iodized oil, into the spinal subarachnoid space is fraught with the danger of producing a foreign body reaction. Arachnoiditis is a serious and not infrequent sequela of myelography.[1]

In an effort to develop a technique of myelography which avoids the introduction of irritating foreign substances, experiments were performed on rabbits and dogs, using a gamma emitting radioisotope (I^{131}). The scintiscanner, which has been described in a previous publication,[2] was used to record the gamma quanta emanating from the I^{131}.

Preliminary experiments on animals, using carrier-free sodium iodide, revealed that with the intrathecal administration of 100 microcuries of sodium iodide, a visual outline of the subarachnoid space could be obtained. However, the sodium iodide diffused very rapidly throughout the cerebrospinal fluid and quickly disappeared from the subarachnoid space.

Iodinated human serum albumin (I*HSA) was then substituted as the tracer agent.* I*HSA is a homologous serum protein which is tagged with I^{131}. The solution contains 5 mg. human serum albumin per ml. of fluid. Better results were obtained with this material since I*HSA has a slower rate of diffusion and is not removed from the subarachnoid space as rapidly as the sodium iodide.

Lumbar laminectomies were then performed on rabbits and a ligature snugly tied around the dural sac and its contents, producing complete block. I*HSA was then introduced into the subarachnoid space, under direct vision, distal to the point of ligature. Scanning of the spine in vivo clearly and accurately demonstrated the site of the experimental lesion. Once these preliminary

From the radioisotope unit, Wadsworth Hospital, Veterans Administration Center, Los Angeles, and the departments of medicine, radiology and surgery, University of California at Los Angeles.

*United States Atomic Energy Commission Authorization No. 16625.

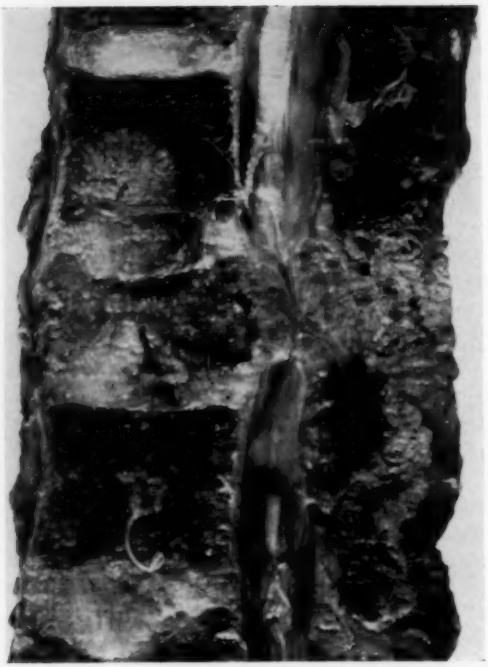
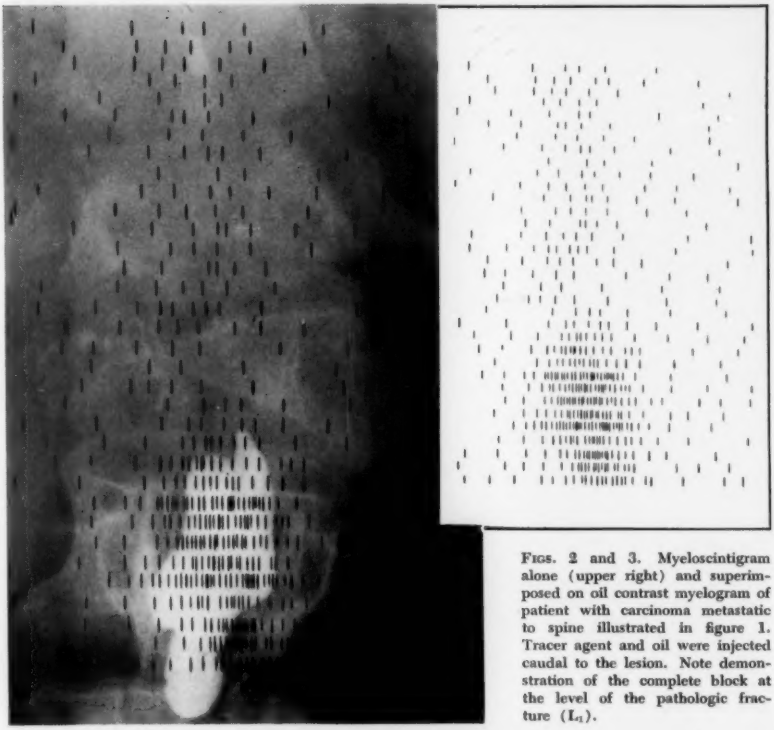


FIG. 1. Autopsy specimen of the patient with carcinoma metastatic to the lumbar spine. Note the collapsed vertebra (L_4) with extension of the tumor producing a complete block.

observations had been completed and the feasibility of the procedure demonstrated, the technique was then applied to patients.

PROCEDURE

The patient is prepared in the conventional manner and a lumbar puncture is performed. A 100 microcuries dose of I*HSA is drawn into a Record syringe and is injected through the spinal needle into the subarachnoid space. The average volume injected varies from 0.2 to 1.0 ml. and depends upon the specific activity of the solution. Thus, if the solution is used before much decay of the I^{131} has occurred, a smaller volume of solution is required than is the case when several days have elapsed since its preparation. In order to dispense the I*HSA evenly in the subarachnoid space, both caudad and cephalad, spinal fluid is slowly withdrawn into the syringe and re-injected two or three times. The needle is then removed and the patient is placed supine upon a level examining table. The automatic scanner is brought into position so that the scintillation counter surveys the area to be scanned. The number of counts per second per stroke on the automatic scanner is set to obtain the maximum contrast be-



FIGS. 2 and 3. Myeloscintigram alone (upper right) and superimposed on oil contrast myelogram of patient with carcinoma metastatic to spine illustrated in figure 1. Tracer agent and oil were injected caudal to the lesion. Note demonstration of the complete block at the level of the pathologic fracture (L_1).

tween the subarachnoid space and "background." The entire procedure, including lumbar puncture, is completed in 15 to 20 minutes.

MATERIAL AND RESULTS

The first patient subjected to this procedure had carcinoma metastatic to the lumbar spine with paraplegia and a complete block at L_1. The lesion was verified at autopsy (figure 1). Myeloscintigrams were performed on this patient, both by the lumbar and cisternal route of injection of I*HSA. The lesion was clearly demonstrated on both scintigrams (figures 2 and 3).

After successful demonstration of a complete block, myeloscintigrams were performed in eight patients suspected of having protruded intervertebral discs.

Oil contrast myelograms demonstrated filling defects on these patients. Protruded intervertebral discs were found at subsequent operation in five of eight patients. The remaining three patients have not as yet been operated upon. In the five patients with verified lesions, excellent correlation between

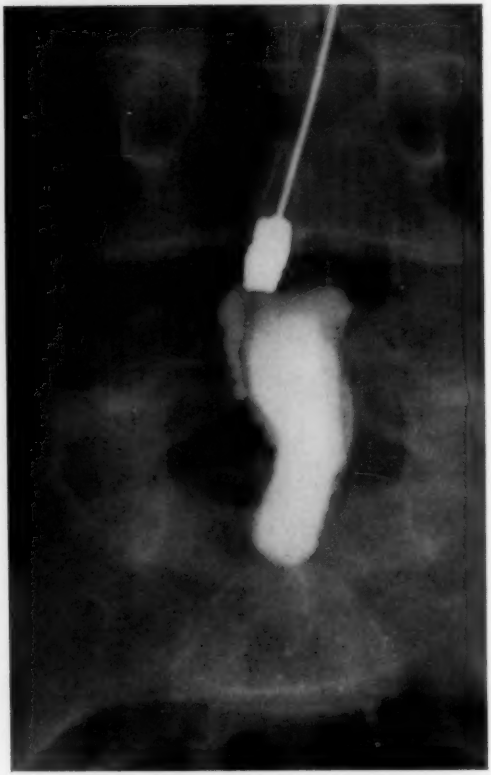


FIG. 4. Oil contrast myelogram on patient with verified lumbosacral protruded intervertebral disc on the right. Note lumbosacral filling defect.

the oil contrast myelogram and the myeloscintigram was observed (figures 4, 5 and 6).

DISCUSSION

I*HSA is a homologous protein and has been widely used for diagnostic studies in man. Its value in the determination of blood volume[3] and cardiac output[4] has been established. It is also used in the diagnosis and localization of brain tumors[5] and for the diagnosis of metastatic cancer of the liver.[6] Since it is derived from a constituent of normal human plasma by methods which do not appreciably alter even its immunologic properties,[7] the tagged serum albumin seems to satisfy the most stringent biological requirements for a diagnostic agent.

The removal of constituents of plasma from the cerebrospinal fluid has been studied. Kottman[8] observed that horse serum injected into the cistern of the

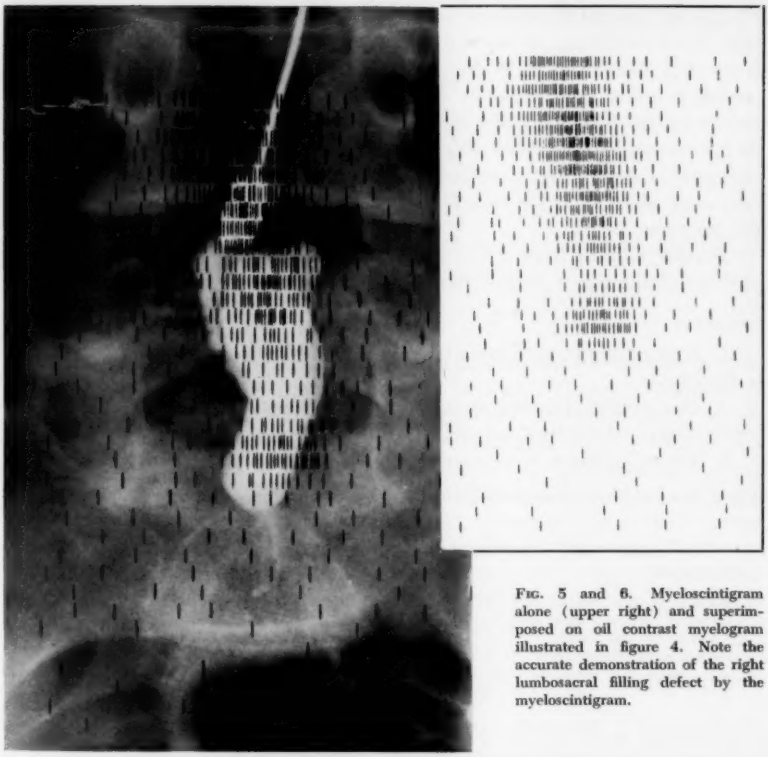


FIG. 5 and 6. Myeloscintigram alone (upper right) and superimposed on oil contrast myelogram illustrated in figure 4. Note the accurate demonstration of the right lumbosacral filling defect by the myeloscintigram.

rabbit disappeared in two days. The horse serum appeared in the blood in one to two hours and reached its maximum concentration in the blood on the second or third day ofter intrathecal injection.

Repeated scanning of the patients in this study revealed that the I*HSA disappears from the subarachnoid space in 24 hours. Since not more than 2 per cent of the I^{131} in I*HSA is present as free iodide,[7] accumulation of I^{131} in the thyroid gland is unlikely. However, potassium iodide has been administered routinely as Lugol's solution 24 hours prior to performing the procedure to prevent accumulation of the free I^{131} in the thyroid gland.

The dose of I^{131} used in this procedure is comparable to the dose employed until very recently for thyroid function studies. Since dilution of I*HSA occurs in the cerebrospinal fluid and since the central nervous system is radio-resistant,[9] radiation hazard is minimal.

The myeloscintigram has several advantages over conventional myelography. The introduction of irritating foreign contrast media, such as iodized oils, is avoided. Since the I*HSA does not have to be removed, the discomfort to the patient is markedly decreased. The scanned area is visualized during the procedure so that if a technical error should occur this is evident immediately. If an error occurs during conventional myelography, it will be apparent only after radiographs have been developed. The procedure may also be repeated, if necessary, since no trace of I*HSA is demonstrable 24 to 48 hours following the injection.

Further clinical trials are in progress to establish the diagnostic reliability of this technique as a routine clinical procedure.

SUMMARY

1. A new technique of myelography using iodinated human serum albumin is described.

2. The results obtained compare favorably with the results observed by conventional oil contrast myelography.

3. The advantages of this technique are discussed.

The authors wish to express their gratitude to Miss Ruth Cordish who prepared the illustrations.

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Romberg has remarked that "a predisposition to Migräne is afforded by the female sex." M. Labarraque observes that "women have the sad privilege of being much more subject to the malady than men," which he attributes to the greater susceptibility of the female nervous system. M. Calmeil is of the same opinion – "Migraine," he says, "is much more frequent with women than men; and as it is often hereditary, it seems lawful to conclude that the constitution and primitive conformation of the Nervous system predispose to this kind of Neurosis." M. Lebert says the same.

Edward Liveling in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Muscle Action Potentials in Myopathies With Special Regard to Progressive Muscular Dystrophy

Paolo Pinelli, M.D. and Fritz Buchthal, M.D.*

IN PREVIOUS INVESTIGATIONS it has been demonstrated that the electromyogram can contribute to the differential diagnosis between muscular atrophies of myogenic and of neurogenic origin.[1] Histologically, myogenic atrophies are characterized by involvement of many muscle fibers from different motor units, and contraction tension is correspondingly reduced. Moderate and strong effort are, therefore, accompanied by the simultaneous recruitment of many fibers to produce an electromyographic pattern essentially like that of normal muscle. In atrophy of neurogenic origin, characterized histologically by the total loss of entire motor units with corresponding "mute areas" on electromyography, a similar moderate or strong voluntary effort brings about an entirely different pattern of discharge. Individual action potentials of motor units near the electrode can be led off without interference from the responses of neighboring units, as occurs only with slight effort in normal muscle (table 1).

Apart from this general electromyographic pattern recorded during maximum effort at low speed, the duration, amplitude and shape of the individual action potentials recorded at high speed during weak voluntary contraction reveal differences of diagnostic significance. In muscular atrophies of neurogenic origin, there is an increase in action potentials of long duration.[1] A reduction in mean duration has been described as characteristic of progressive muscular dystrophy and other myopathies.[2]

However, the finding of action potentials of long or short duration is not in itself specific for any pathologic condition, since a wide range of action potentials, both extremely short and long, is recorded from normal muscle during voluntary activity. This has been found to be the case independent of the type, shape and dimensions of the electrode used for leading off. Therefore, comparisons between action potential duration in normal and atrophic

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*Working with a fellowship from the Rask-Örsted Foundation.

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TABLE 1
DIFFERENTIATION OF NEUROGENIC AND MYOGENIC ATROPHY
Electromyographic patterns on low speed recording during maximal effort

Muscular atrophy of of	*Severe clinical atrophy degree of activity 0 to 2*[5]				*Mild clinical atrophy degree of activity 2.5 to 3*[5]			
	Number of muscles examined	*Patterns in per cent* I	T	S	*Number of muscles examined*	*Patterns in per cent* I	T	S
Myogenic origin	53	76	13	11	29	90	10	0
Neurogenic origin	204	2	27	71	60	12	65	23

Definition of electromyographic patterns: I = Interference, simultaneous activity of many fibers. T = Transitory state, similar to I, but with the number of fibers so reduced that the discharges from the subunits nearest to the electrode are distinguishable. S = Single oscillations, individual action potentials, without interference from the responses of adjacent subunits.

muscle can only be made on a statistical basis. Distribution curves (histograms) for the durations of a sufficient number of action potentials must be compared from normal and from atrophic muscle.

The present investigation deals with a study of histograms of duration and amplitude of action potentials in progressive muscular dystrophy, congenital myotonia (Thomsen and Steiner), disuse atrophy, myasthenia gravis, and other myopathies; and their correlation with clinical and biopsy findings.

METHODS

Action potentials were led off from two separate points of the muscle using three types of electrode: unipolar, concentric and bipolar. Data as to electrodes, recording procedure, intramuscular temperature control, definition of action potential parameters and statistical treatment of the results have been described in detail.[3,4] The classification of electromyographic patterns recorded at low speed during maximum effort is defined in table 1. The various action potential shapes recorded at high speed during weak effort are defined and illustrated in figure 4. Measurements were made of total action potential duration and of peak to peak amplitude. Histograms of these values were constructed, and compared with histograms based on action potential measurements from the corresponding normal muscles of subjects matched for age. Two to five dystrophic muscles were examined in each patient. Whenever possible, a biopsy was obtained from the region of the muscle previously examined electromyographically. The histologic examinations were kindly performed by Erna Christensen, M.D., laboratory of neuropathology, Institute of Pathology, University of Copenhagen.

RESULTS

1. *Progressive muscular dystrophy*

Thirty-two hospitalized patients suffering from progressive muscular dystrophy were examined. In 29 cases, the atrophy was localized to the proximal muscles of the upper and lower limbs (variety Duchenne and Leyden, Möbius). In three cases, the distal muscles of the upper limb were affected as well.

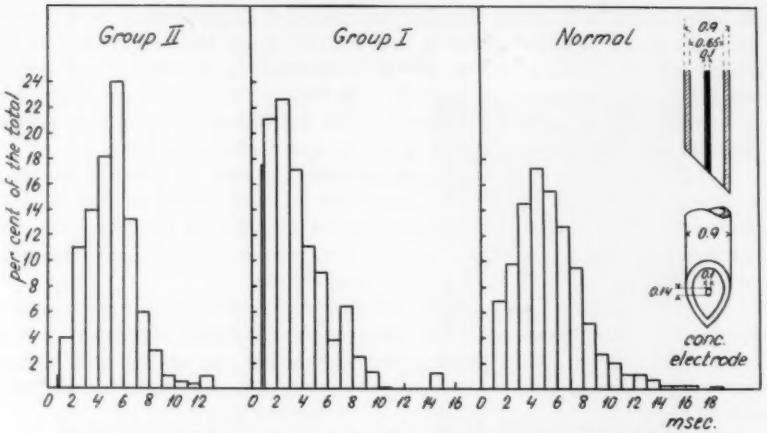

FIG. 1. Percentage distribution of action potential duration (ordinate) at millisecond time intervals (abscissa) for group 1 (increased percentage of short action potential duration: total number of action potentials 1317); group 2 (slightly increased percentage of long action potential duration: total number 293) and normals (total number of action potentials 507). The concentric needle electrode used for recording is illustrated to the right.

In all cases except two, the disease had persisted for more than two years and was rather advanced. An obvious familial tendency was found in 15 cases. Detailed information about the genetic background of the patients presented here is given by Levison.[5] A muscle biopsy was performed in 17 patients and was the basis of the clinical diagnosis in the two cases in which the disease was at an early stage.

In agreement with former observations, an electromyogram recorded at low speed (4 to 5 cm./sec.) revealed in most muscles an interfering pattern of action potentials during moderate or maximum effort. Exceptions were some muscles with extremely advanced atrophy; these showed in addition large mute areas: not all the points recorded in a muscle necessarily give rise to the same degree of activity. During weak effort, action potentials recorded simultaneously from two different points of the same muscle never showed a significant degree of coincidence, or synchronization. Fibrillation activity was never observed, and insertion activity was seen only once in a muscle with a severe degree of atrophy.

The 32 cases examined fell into two groups on the basis of differences in *mean action potential duration*:

1. Those with decreased mean duration.
2. Those with normal or increased mean duration.

In the 21 cases of group 1 there was a statistically significant decrease in mean action potential duration (figure 1). In half of these (ten cases), all muscles gave a statistically significant decrease; in the remaining (11 cases), a significant decrease in mean duration was found in some of the dystrophic muscles examined. Excluding polyphasic potentials (> 4 phases), the average mean action potential duration in dystrophic muscles was found to be 25 per cent less than in normal muscle. When the polyphasic potentials were

included in the calculation, the decrease averaged 22 per cent. The decrease in mean action potential duration was not due to an altered distribution of action potential shapes; it was due to a decrease in duration of all action potentials, but mainly of the diphasic. The findings in group 1 are illustrated in a representative patient (figure 2), with the histogram of muscle action potential duration, muscle biopsy and low speed electromyogram.

Comparing mean values of action potential duration in different muscles, a significant decrease in duration was found in 14 of 20 biceps muscles (70 per cent) and in seven of 22 femoral quadriceps muscles (32 per cent). It is interesting in this connection that the arm muscles normally have a lower mean action potential duration than the leg muscles.

The 11 patients in group 2 had normal or increased values for mean action potential duration (figure 1). The increase was statistically significant in five cases. The average mean action potential duration was 15 per cent higher than that in normal muscle; excluding the polyphasic potentials, the increase was 14 per cent.

Histograms of duration of action potentials from all muscles of the two groups studied with a concentric electrode are given in figure 1 and compared with the histogram from corresponding normal muscles. Findings with unipolar and bipolar electrodes did not differ significantly when the percentage change between pathologic and normal muscle was compared.

In the measurements given in the curves, the position of the different types of electrodes was random in relation to the axis of the muscle fiber. In normal muscle, the mean duration was lower when the electrode lay parallel to the axis of the muscle fibers than when it lay perpendicularly. In a special series of measurements with systematic variation of the position of the electrode, this difference did not appear in dystrophic muscles.

Examination of the data with respect to *mean amplitude of the action potentials* showed that muscles with small action potential duration (group 1) had a mean amplitude within normal limits. Muscles with normal or increased duration (group 2) had an increase in amplitude of approximately 130 per cent. Although the distribution curves for action potential amplitude were less homogenous than those for duration, the differences in mean amplitude in the two groups were nevertheless statistically significant.

Repeated examinations of the same muscle gave approximately the same mean value of duration and amplitude and this reproducibility was also obtained when the repeat recording was made after an interval of as long as one year. This applies both to cases from group 1 and group 2.

The distribution of *different shapes of action potentials* did not differ much from that of normal muscle (figures 3 and 4). This was the case for the different types of electrodes and different muscles. There was only a slight increase in diphasic action potentials at the expense of triphasic in group 1. Action potentials with more than four phases (polyphasic potentials) occurred in 7 per cent of all action potentials in muscles of group 1 and in 12.5 per cent in muscles of group 2. In both groups, they occurred in 341 of 4258

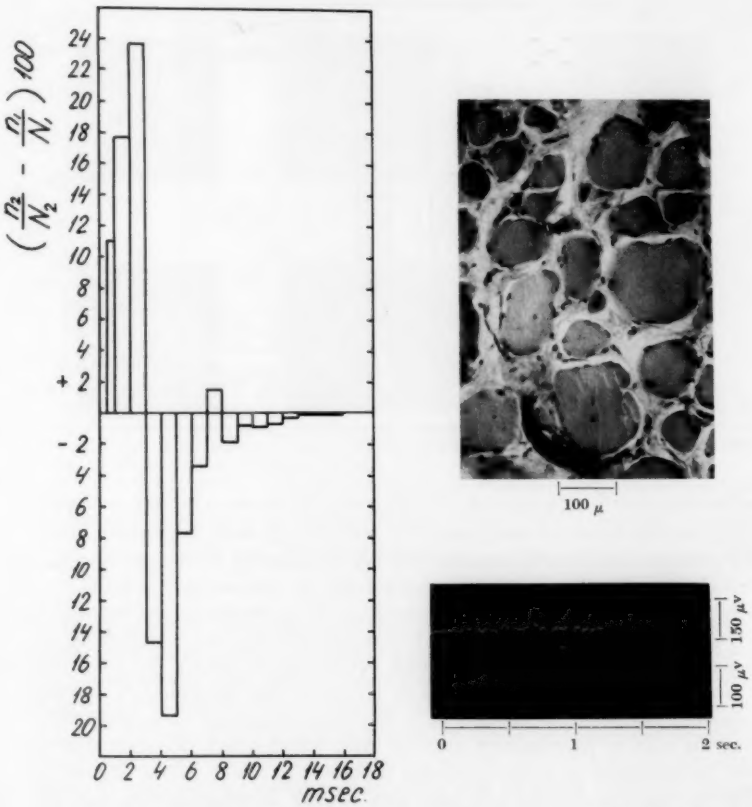

FIG. 2. *Distribution of action potential duration, biopsy and electromyogram* of the right brachial biceps muscle in a case of progressive muscular dystrophy, group 1 (degree of activity*=1). Male age 12, onset of symptoms at about three years of age. No family history of muscular dystrophy. At present, paresis and atrophy of all back muscles, severe paresis of shoulder girdle muscles and proximal arm muscles; pseudohypertrophy of quadriceps and triceps surae. *Left*: difference between the distribution of action potential duration in dystrophic and in normal muscle. Columns above the zero line indicate the percentage increase in short action potentials in dystrophic as compared with normal muscle; columns below the zero line indicate the corresponding percentage decrease in long action potentials. The mean action potential duration was 40 per cent shorter than in normal muscle. N_2=93, number of action potentials in dystrophic muscle. N_1=78, number of action potentials in normals, same age corresponding muscle. n_1 and n_2=number of potentials per interval of duration. *Upper right*: biopsy. *Lower right*: electromyogram, two leads, recorded at low speed, pattern of interfering activity at maximum effort.

action potentials, or 8 per cent. In normal muscle, polyphasic action potentials represent 1 to 3 per cent of all action potentials. The polyphasic potentials were mainly those with short spike duration, while the grouped polyphasic potentials, with the spike duration of the normal triphasic potential,

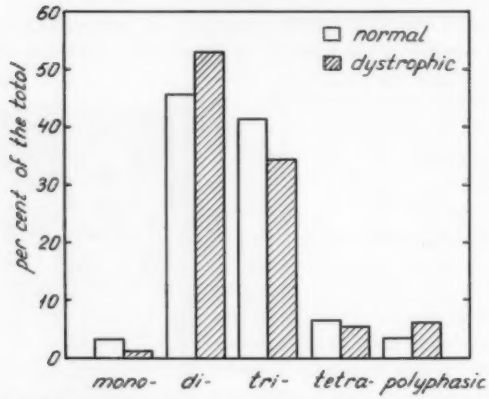

FIG. 3. Percentage distribution of various action potential shapes in normal muscles (692 action potentials) and in dystrophic muscles of group 1 with decreased mean action potential duration (953 action potentials). Concentric electrode recording.

were less frequently represented. Muscles with an increased number of polyphasic potentials tended to be those with mild atrophy both in groups 1 and 2.

An attempt was made to correlate the action potential findings with pathologic and clinical findings. Positive correlations are summarized in table 2.

The two groups differed in the occurrence of an *inflammatory reaction* in the biopsy. This was seen in six of 17 biopsies and was characterized by the presence of lymphocytes and histiocytes. With one exception, an inflammatory reaction was confined to patients of group 1. The inflammatory reaction was distinct but never as distinct as in the cases described as polymyositis.[3] As was the case in polymyositis, muscles with inflammatory reaction showed a clear displacement of action potential durations to lower values (figure 5).

The two groups differed not only with respect to inflammation, but also with respect to *heredity* (table 2). There was an increased occurrence of obvious familial predisposition in the cases with increased or normal mean duration of group 2, as compared with group 1.

Other positive correlations with action potential parameters occurred within group 1. A significant decrease in action potential amplitude was accompanied by a relatively high degree of atrophy. Furthermore, the decrease in action potential duration was more pronounced when the disease had lasted for more than 15 years.

TABLE 2

POSITIVE CORRELATIONS WITH MEAN ACTION POTENTIAL DURATION IN PATIENTS WITH PROGRESSIVE MUSCULAR DYSTROPHY

Mean duration	*Inflammation on biopsy*	*Positive family history*
Decreased (group 1)	60% (6 of 10 cases)	29% (6 of 21 cases)
Increased (group 2)	14% (1 of 7 cases)	56% (5 of 9 cases)

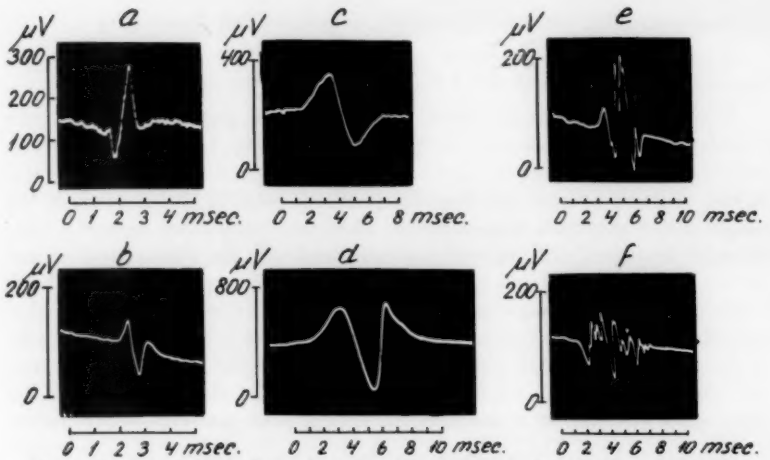

FIG. 4. Examples of various shapes of muscle action potentials recorded with the concentric electrode in dystrophic muscles. *a*) diphasic, *b*) triphasic action potential, short duration, small amplitude dominating the spectrum of action potentials in muscles of group 1. *c*) *and d*) diphasic and triphasic action potentials respectively, but with longer duration and higher amplitude than *a*) and *b*), characteristic of muscles of group 2. *e*) and *f*) potentials with more than four phases — polyphasic action potentials. The oblique x-axis in records *b*, *e* and *f* is due to slow movement of the film during the sweep time.[3]

The degree of reduction in action potential duration, however, was not correlated with the degree of atrophy, whether manifested clinically or electromyographically. Specifically there was no correlation between the number of subunits*[3,4] recordable in a given area and reduction in action potential duration. Groups 1 and 2 were similar with respect to muscular atrophy and activity,[6] with respect to mean patient age and to mean duration of the disease. With the exception of inflammation, there was no other histologic difference between the muscles of the two groups. The distribution of fiber diameters, the number of hypertrophic fibers, and the degree of proliferation of connective and fatty tissue were equal in the two groups. The degree of pathologic involvement of the muscle corresponded, on the whole, to the clinical degree of atrophy.

2. *Dystrophia myotonica and myotonia Thomsen*

In three cases of dystrophia myotonica (Steinert), a significant decrease in mean duration of the action potentials was found in all muscles investigated. The decrease averaged 45 per cent of the duration in normal muscle. The mean action potential amplitude was within normal limits. These findings correspond to those in cases of progressive muscular dystrophy in group 1.

In an advanced case of myotonia Thomsen without atrophy, the mean action potential duration was normal.

*Subunit denotes adjacent fibers belonging to the same motor unit.[4]

3. *Disuse atrophy, muscular hypoplasia, amyotonia and hypotrophy*

A study of these cases seemed of interest, since they might contribute information as to the specificity of the findings in dystrophic muscle.

Disuse atrophy: No consistent change in action potential duration was found. In seven cases, a mild atrophy (mean activity 3) was caused by inactivation of an extremity in plaster of Paris for a period of one to six months. In two of these, a significant decrease (−30 per cent) in the duration of the simple action potentials was observed, while two other cases showed a considerable increase (+30 per cent) as compared with the symmetrical normal muscle. The remainder fell within normal limits. The number of polyphasic action potentials (figures 4e and 4f) was increased in almost all these muscles, representing 25 per cent of all action potentials recorded. They were chiefly of the grouped polyphasic potential type, with the spike duration of the normal triphasic potential. When they were included in the calculations of the mean value of duration, a significant increase (+ 59 per cent) was found in four of seven cases. The mean amplitude of the action potentials was within normal limits.

In a case of *unilateral hypoplasia* in a 16 year old girl with a cortical birth lesion, the mean action potential duration in the m.flexor digitorum communis was identical with that of the symmetrical normal muscle. A normal duration was also found in three cases of *congenital encephalopathy* (one to four years old) accompanied by a generalized muscular atrophy of moderate degree.

The mean duration of muscle action potentials in three cases of *congenital amyotonia* was significantly increased in the advanced stage of the disease, while the mean amplitude was considerably reduced. In these cases, there were no signs of neurogenic atrophy in the biopsy. Also in less severe cases, action potentials with a duration of < 4 msec. occurred rarely, whereas in normal muscle they comprise 20 to 55 per cent of the total.

On the other hand, in a case of extreme *generalized atrophy* (a 13 year old anorexic girl) with no biopsy signs of dystrophy or neurogenic atrophy, the mean action potential duration was significantly decreased as compared with the corresponding normal muscle (23 per cent). This decrease was mainly caused by an increased representation of short regularly shaped diphasic action potentials.

4. *Palpable muscle alterations (myosis, fibrositis)*

In 11 muscles from five cases, the mean action potential duration was within normal limits. It is, however, worth noting that the mean amplitude was significantly increased by 100 per cent in seven muscles from three cases as compared with the mean amplitude of action potentials in normal muscle.

5. *Myasthenia gravis*

The cases examined had pronounced signs of myasthenia and were not

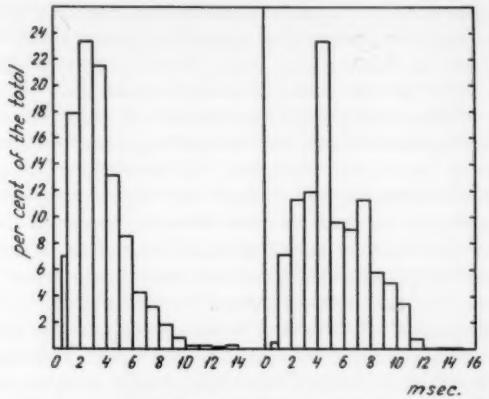

FIG. 5. Histograms of action potential duration in progressive muscular dystrophy. *Left curve*: action potentials in muscles *with* inflammation on biopsy. (Number of action potentials: 156). *Right curve*: action potentials in muscles *without* signs of inflammation. (Number of action potentials: 136). Concentric needle electrode.

under the influence of anticholinesterases during the electromyographic examination.

Among muscles examined from six cases, a decreased mean duration (19 per cent) was found in two cases. The mean amplitude was within normal limits. Biopsies taken in two cases showed normal conditions and especially no signs of dystrophy or lymphocytic infiltration.

DISCUSSION

The delineation of two groups of dystrophic patients, those with decreased and those with normal or increased mean action potential duration, has interesting implications. It suggests a possible difference in pathogenesis. Progressive muscular dystrophy is generally considered an hereditary disease of the dominant type; the cases with a negative family history (35 per cent) have been considered to be hereditarily recessive. A thorough hereditary analysis of the cases presented here[5] revealed a higher familial tendency in cases from group 2 (56 per cent) than in those from group 1 (29 per cent) (table 2). In none of the cases with a negative family history could signs of a recessive tendency be discovered. This finding appears reliable in a small country in which the difficulties in follow-up are less pronounced than in a larger and less stable population.

Cases of group 1 with short action potential duration, on the other hand, showed a higher incidence of inflammatory reaction (60 per cent) than did cases of group 2 (14 per cent) (table 2). In view of the constant correlation between inflammatory response and short action potential duration in chronic

and acute polymyositis,[3] it appears possible that the inflammatory reaction may be the precursor of dystrophy in muscles of group 1 and that these dystrophies may have an inflammatory rather than a genetic etiology. Although no decisive evidence for this assumption can be offered as yet, a case may be mentioned in which a microscopic examination of muscle tissue showed an extreme degree of infiltration and the histogram gave a significant decrease in mean duration of the action potentials. A repeated biopsy one year later showed diffuse dystrophic changes without any sign of inflammatory reaction, while the reduction in the mean duration remained unchanged.

The study of the duration, amplitude and shape of the action potentials in different myopathies has revealed conditions considerably more complex than has been assumed in former investigations on this subject.[2,7] As already emphasized, the finding of a decrease in mean action potential duration was by no means specific for progressive muscular dystrophy. It occurred regularly in dystrophia myotonica (Steinert) and sporadically in disuse atrophy, myasthenia gravis and a case of generalized atrophy due to malnutrition. It was not quantitatively correlated with the degree of atrophic and dystrophic change on biopsy nor was there any correlation between the number of subunits recordable from a given area and the decrease in mean action potential duration. A decrease can, in fact, occur without atrophy or dystrophy as is exemplified by the findings in acute and chronic polymyositis.[3]

No simple explanation can be offered for the cause of the displacement of action potential durations to lower values in certain cases of dystrophy and other myopathies. Inflammatory reaction in itself cannot be the direct cause of shortened duration, since there were muscles which had the same decrease in duration without signs of inflammation. Nor can the change in muscle fiber diameter be directly correlated with the reduction, in view of the inconsistent findings in disuse atrophy.

Random loss of fibers within the subunit* can also hardly account for the reduction in mean duration, since dystrophy and atrophy may occur to a severe degree in the presence of normal mean duration. One should also take into consideration that random loss should give rise to an increase in polyphasic action potentials as well. Although this occurs, the increase in polyphasic action potentials is far less pronounced in progressive muscular dystrophy (8 per cent) than in disuse atrophy (25 per cent) where the loss of fibers must be assumed to be less, the degree of activity being higher (3)* than in progressive muscular dystrophy (2).*

Selective loss of fibers within the subunit due to involvement of adjacent motor end plates might theoretically also reduce action potential duration by decreasing the temporal dispersion of the summated action potential. Evidence implicating end plate affection is conflicting, however. In myasthenia gravis, where end plate affection is known to exist, there is no consistent change in action potential duration. It is true that all of six cases of dystrophy with short action potential duration had, as occurs in myasthenia, decreased acetyl-

choline sensitivity.[8] However, the one case of dystrophy examined from group 2 with normal action potential duration had a similar decrease in acetylcholine sensitivity.

In evaluating the changes in mean action potential amplitude, it must be born in mind that only loss of a large part of the fibers within a subunit results in a significant change in action potential amplitude, amplitude being much less sensitive to loss of fibers than duration.[4]

The various explanations for short action potential duration in polymyositis have been discussed.[3] In contrast to the findings there, however, the short mean duration of action potential in dystrophy is not associated with a marked increase in the relative occurrence of diphasic potentials. Therefore, change in the functional length of the fiber, which appeared to be one of the factors causing short action potential duration in polymyositis, cannot be assumed to play an essential rôle in causing potential duration changes in dystrophy. Since neither atrophy, inflammation, nor shortening in the functional length of the fiber provides a satisfactory explanation for the short duration, it seems most reasonable to assume a general increase in propagation velocity of the impulse over the muscle fiber. This might be the consequence of an existing or previous inflammatory reaction.

PRACTICAL APPLICATION

Both action potential analysis and the electromyogram recorded at maximum effort and low speed of recording can contribute materially to the differentiation between neurogenic and myogenic atrophy. It is, however, necessary to realize that neither is an infallible aid.

The presence of a significant decrease in mean action potential duration points in favor of polymyositis or progressive muscular dystrophy. Neurogenic atrophy, on the other hand, tends to be associated with an increase in action potential duration.[1] Since, however, certain peripheral neurogenic atrophies showed normal durations, just as did one third of the patients with progressive muscular dystrophy, action potential analyses may be of no positive diagnostic assistance in certain individual cases. Furthermore, in view of the wide spread of action potential durations in normal muscle, diagnostic conclusions should be based on a statistical analysis of action potential parameters. It is especially worthy of emphasis, therefore, that "observation of the action potential picture on the screen of the oscillograph, without measurement from tracings," as stated by Kugelberg[2] to be sufficient, may be actually misleading from a diagnostic point of view.

With respect to the electromyogram recorded at low speed during moderate to maximum effort, the results from the examination of all atrophies of myogenic and neurogenic origin (degree of activity[6] < 3) are summarized in table 1. In myogenic atrophies, interference (I) was found in 81 per cent, transitory state (T) in 12 per cent, and single oscillations (S) in 7 per cent of the muscles examined (definitions in table 1). In neurogenic atrophies the corresponding percentage figures were 5 (I), 35 (T) and 60 (S).

Thus, single oscillations during maximum effort, considered typical for the presence of neurogenic atrophy, occurred only exceptionally in progressive and myotonic dystrophy, and then only in cases with extremely advanced atrophy (degree of activity[6] 0-1).

SUMMARY

1. 32 cases of progressive muscular dystrophy fell into two groups according to the mean duration of action potentials: group 1 with a statistically significant decrease in action potential duration (−25 per cent in 21 cases); group 2 with a normal or increased mean duration in all muscles examined (+8 per cent in 11 cases).

2. As compared with normal muscle, the mean amplitude of the action potentials was increased in muscles of group 2 (+130 per cent).

3. In muscles with short action potential duration (group 1), there was a slight increase in the occurrence of short diphasic potentials at the expense of triphasic. In some dystrophic muscles, equally distributed in both groups, there was an increased occurrence of polyphasic potentials (> 4 phases). They averaged 8 per cent of all potentials. In muscles with disuse atrophy, action potentials with more than four phases occurred in 25 per cent of all action potentials. These figures may be compared with the 1 to 3 per cent incidence of polyphasic potentials in normal muscle.

4. Dystrophic muscles with histologic signs of an inflammatory reaction fell in the group 1 with a significant decrease in mean action potential duration. A positive family history was more frequently obtained in patients of group 2 with normal or increased action potential duration. These findings suggest that progressive muscular dystrophy may be divisible into two groups: one of primarily inflammatory and another of primarily genetic pathogenesis. This suggestion would have to be confirmed on a larger patient population.

5. Findings from action potential analysis are represented for other myopathies:

a) Patients with dystrophia myotonica showed a short mean duration of action potentials, whereas congenital amyotonia was associated with an increase.

b) Findings as to mean duration were inconsistent in patients with myasthenia gravis and disuse atrophy.

c) No significant deviation from normal duration of action potentials was found in myotonia Thomsen or palpable muscle alterations (fibrositis). The latter showed, however, an increased action potential amplitude as compared with normal muscle.

6. The possible causes for the displacement of the distribution curve of action potentials to lower values of duration are discussed. An increase in propagation velocity of the impulse along the fibers appears to be the most likely explanation.

7. Practical application of findings from action potential analysis and from low speed electromyography are discussed as they apply to the differential diagnosis of myogenic and neurogenic atrophy.

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At the onset of the severe fit the spasm is tonic in character, rigid violent muscular contraction, fixing the limbs in irregular positions. There is usually deviation of the eyes and rotation of the head towards one side, and this rotation may involve the whole body, and sometimes cause the patient to turn round, even two or three times. The tonic spasm involves the muscles of the chest and abdomen. The features are distorted; the face, usually at first pale, becomes suffused and then livid, as the chest is fixed and respiratory movements are arrested. The eyes are open or closed; the conjunctiva is insensitive; the pupils dilate widely as cyanosis comes on. As the spasm continues, it commonly changes in its relative intensity in different parts, so that slight changes in the position of the strained limbs occur. Presently, when the cyanosis has become intense, the fixed tetanic contractions of the muscles can be felt to be vibratory, and the vibrations increase to slight visible remissions. As these remissions become deeper, the muscular contractions become more shock-like in character, and the stage of clonic spasm is reached, in which the limbs, head, face, jaw, trunk are jerked with violence. In the resulting movement of the chest, air is expelled from the thorax, and bloody saliva is frothed out between the lips. The air entering the lungs is at first insufficient to lessen the lividity, and the patient may seem to be at the point of death. But as the intervals between the shocks of spasm lengthen, and the remissions become greater, more breath enters the chest, and the lividity lessens. In becoming less frequent, the muscular contractions do not become less strong, and the last jerk is often as violent as those which have preceded it. At last the spasm is at an end, and the patient lies senseless and prostrate, and usually sleeps heavily for a time, and then can be roused. Urine frequently, and fæces occasionally, are passed in the fit.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Minor and Major Tremor

Results in 544 Treated Cases

Lewis J. Doshay, M.D., Kate Constable, M.D.
and Adolpho Zier, M.D.

PARKINSON in his historic paper[1] of 1817 on "The Shaking Palsy" was the first to call attention to the challenge to treatment that tremor presents. In spite of great progress in other fields of medicine the problem has not lessened to any appreciable degree since that time. Patients with pronounced forms of Parkinson tremor continue to suffer despite all the advances in therapy of the past decade. The problem, moreover, is assuming increasing concern to specialists and general practitioners, because the severest form of tremor occurs in elderly patients who are accumulating in vast numbers as a consequence of the increase in the life span.

Tremor, moreover, is not only a problem in itself, but it is accompanied by a train of disturbing complications including severe sweating, insomnia, loss of weight, fatigue and depression. The belladonna drugs, antihistamines and related compounds provide relief to some cases, but disturbing side reactions and changes in tolerance limit their use in many patients. Heroic measures have been used by neurologic surgeons in an attempt to check tremor, but since the underlying pathophysiology is unknown, it is difficult to know where and what to cut. The results thus far have not been satisfactory.[2,3,4] We are still groping in the dark and medical therapy rests almost entirely on an empiric basis.

ANALYSIS OF CASE MATERIAL

It is the purpose of this paper to present a survey of the results obtained in tremor among 520 patients with parkinsonism who were treated with various medicaments during the past three years, and to present the results obtained in a preliminary trial of one of several new drugs. In 216 the symptoms were attributed to arteriosclerosis, in 133 to unknown causes, and in 171 they were the sequel of encephalitis lethargica. The youngest patient was 14 and the oldest 84 years of age. There were 313 male and 207 female patients.

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TABLE 1

AGE DISTRIBUTION IN 520 CASES OF PARKINSON TREMOR

Age (years)	*Total*		*Arterio-sclerotic*		*Idio-pathic*		*Post-encephalitic*	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Below 30	17	3					17	10
30 to 40	79	15			3	2	76	44
40 to 50	96	18	5	2	40	30	51	30
50 to 60	164	32	58	27	82	62	24	14
60 to 70	134	26	123	57	8	6	3	2
Over 70	30	6	30	14				
Total	520	100	216	41	133	26	171	33

Almost two thirds of the 520 cases were past 50 years of age and one third past 60 (table 1). For reasons unclear, the severest type of tremor was found predominantly in these elderly patients and was more common in the male. In addition, the elderly patients are the very ones who possess the least tolerance for drugs, hence correspondingly derive the least benefit from their use. If given small amounts of medication, violent tremors are not appreciably reduced and if large doses are administered, the patients often become so disturbed and excited that the tremor is aggravated. Of further interest is the finding that only 3 per cent of all tremor cases are under 30 years of age and but 5 per cent are over 70 years.

In table 2 one notes that out of a total of 544 cases of parkinsonism under treatment, 520 manifested tremor in some form or degree and only 24 of the cases were free of tremor. Nineteen of the latter, or 80 per cent, belonged to the encephalitic group, with rigidity and oculogyria or other symptoms as the main problem but little or no tremor. In the arteriosclerotic group, three cases were without visible tremor, and in the idiopathic group only two. The high ratio of tremor (98.6) found among the arteriosclerotic patients differs with

TABLE 2

THE OCCURRENCE OF TREMOR AMONG 544 PARKINSON CASES

	Total		*Arterio-sclerotic*		*Idio-pathic*		*Post-encephalitic*	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Tremor absent	24	4	3	2	2	2	19	10
Mild tremor	385	71	121	55	106	78	158	83
Usually unilateral Intermittent Small amplitude Affected by emotion or strain								
Severe tremor	135	25	95	43	27	20	13	7
Bilateral Constant Large amplitude Independent of emotion or strain								
Total	544	100	219	40	135	25	190	35

the findings of others,[5,6] but this is related to the criteria used to determine the presence of tremor. Thus while other investigators may choose to disregard mild forms of tremor, in the current survey every case of rhythmic alternating tremor, whether mild or severe, whether in the resting stage or during effort or excitement, was included.

Experience made it possible to delineate two fairly distinct types of tremor and the patients were classified accordingly (table 2). The mild or minor tremor category included cases in whom tremor was unilateral and manifested itself only on occasions of excitement, strain or effort, or when bilateral, was of small amplitude and of little concern to or effect upon the patient. Cases classified as severe or major tremor were sharply distinguishable from the above. Tremor among these cases is bilateral, continuous throughout the day and almost entirely independent of emotion. It is frequently accompanied by sweating, loss of weight, anorexia, insomnia, weakness, tiredness and mental depression. This type is predominantly found in the arteriosclerotic group or among the very advanced and older patients of the idiopathic group. It should not be presumed, however, that a minor type of tremor cannot bring great misery, depression, insomnia and loss of weight and appetite to certain patients, as in instances where such tremor is responsible for the loss of employment, worries with regard to family obligations and the future outlook. Nevertheless, the tremor per se is entirely different from the severe variety.

On this grading of tremors, 158 of the 385 cases with minor tremor, or 41 per cent, belong to the postencephalitic group. It is of added interest, that only 7 per cent of this group have a severe degree of tremor. This compares with 20 per cent in the idiopathic group and 43 per cent in the arteriosclerotic group. The table thus points up the serious problem of the arteriosclerotic group, especially when so little can be done for these individuals because of their poor tolerance for drugs.

Another phase of the tremor problem is presented in figure 1. Here the primary concern is not so much the severity of tremor, but the mode of onset and course of the tremor in each group. Manifestly, no graph can portray the entire picture, because pronounced variations exist among the individual patients in matters of tolerance, response to drugs, and extent of pathology. For example, even among cases of severest tremor in the arteriosclerotic group, 20 per cent respond favorably to treatment. However, the basic aim of the figure is to portray the comparative tendencies of tremor among patients in the three groups of parkinsonism, so that better insight may be derived in regard to matters of prognosis and therapy. This chart shows that postencephalic tremor increases slowly during the course of 10, 20 or 30 years, rises to a climax bordering on the severest form of tremor and can be ameliorated by therapy. It rarely becomes excessive, possibly because these patients possess tremendous tolerance for all kinds of drugs,[7,8,9] and their tremors can

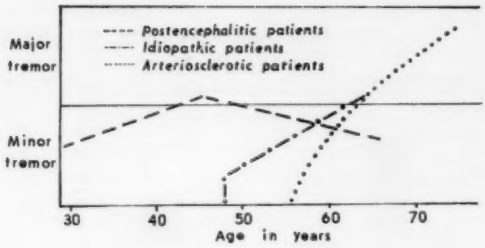

FIG. 1. Graphic presentation of tremor course in 520 cases.

be effectively controlled with one or another type of medication, as the following case will illustrate:

Case 1.—A 36 year old female with postencephalitic parkinsonism was first seen in 1943 when she was extremely emaciated, weighed 82 lbs. and exhibited pronounced tremors, sweating, sialorrhea, lethargy, oculogyria and rigidity. She had great difficulty in walking or standing. She was given atropine and hyoscine, after which her condition improved remarkably, with her weight rising to 101 lbs. She remained completely stabilized for four years, when the effects of atropine began to wear off. Panparnit was then added in small amounts, but had no effect and large amounts caused stomach cramps. Artane was then tried without benefit. In August 1948 Diparcol* was administered and she immediately responded with marked improvement. She continued to be comfortable until March 1949, when the beneficial effects of Diparcol wore off and cramping of the toes, crying, sleeplessness, tremor and rigidity returned to a degree equal to that originally noted. Benadryl was administered but made her more tremulous and upset her stomach. Thephorin was then tried and so was Artane; each failed. In August 1950 she was again given Diparcol and atropine, with hyoscine added, but she continued to feel wretched and her family suffered accordingly. In November 1950 MK-02* was first substituted for atropine and then for atropine and hyoscine. She has continued remarkably well to date on a combination of Diparcol and MK-02. She now weighs 113 lbs.

The curve for the idiopathic group in figure 1 indicates that tremor in these patients usually sets in abruptly and tends to increase rapidly. However, since their tolerance is of a higher order than among arteriosclerotic cases, treatment serves to keep the tremor under fair control for many years. Even so, upon reaching 60 years of age or thereabouts, they commence to show the clinical signs and characteristics of the arteriosclerotic group and from there on their course is more or less indistinguishable from the latter group:

Case 2.—A man aged 59 suddenly developed tremor in his left arm at 50 years of age. The syndrome progressed rapidly. Rigidity was added to tremor and spread to the right extremities, neck and trunk. There was some drowsiness and sialorrhea. He spoke in a monotone. There was no diplopia, strabismus, weakness of convergence, or oculogyria. The clinical picture was typical of idiopathic parkinsonism. Over a period of years he was maintained at first on small amounts of atropine and later on Bulgarian belladonna, Rabellon, scopolamine and Vinobel. His condition remained fairly stationary for periods at

*Diparcol is diethylaminoethyl-N-dibonzoparathiazene hydrochloride. It was developed by the Rhone Chemical Society of Paris and manufactured in this country by Merck & Co., which has since discontinued its production. MK-02 is tropine benzohydryl ether methane sulphate. It is a product of Merck & Co., and is as yet limited to investigational use.

TABLE 3

RESULTS OF TREATMENT AMONG 520 CASES OF PARKINSON TREMOR

Result of Treatment	Total		Minor tremor		Major tremor	
	No.	Per cent	No.	Per cent	No.	Per cent
Improved	294	56	262	68	32	24
Unchanged	68	13	45	12	23	17
Worse	102	20	53	14	49	36
Untraced or unknown	56	11	25	6	31	23
Total	520	100	385	74	135	26

a time. He was able to get about slowly, although he required help with dressing. On rare occasions he would smile, but for the most part he remained disgruntled, irritable and depressed.

At the age of 55 years there developed otosclerosis and gradual evidence of cerebral and generalized arteriosclerosis. Albumin and casts appeared in the urine, and his blood pressure rose to 200 mm. systolic. He began to complain of headache, vertigo and tinnitus. Edema of the ankles and legs appeared, necessitating the recurrent administration of intravenous mercurial compounds.

For the past seven years he spent the winters in Florida. In December of 1947 belladonna and scopolamine were discontinued by a local physician, with the result that the patient became, as his family described it, "stone rigid" and was unable to chew, swallow or speak. He was then placed in a mental institution, where he was fed fluids intravenously, lost considerable weight and was considered moribund. At this point he was placed on Artane therapy, 2 mg. three times a day. There was almost immediate improvement. He began to eat and talk and soon progressed to dressing and shaving himself. He gained weight and was on the mend to the status before his sudden decline. In the latter phase of the illness, this patient could no longer be considered an idiopathic case, but rather a case of arteriosclerotic parkinsonism.

The arteriosclerotic tremor, unlike that of the idiopathic, develops gradually but tends toward a steady rise. The curve in the chart, however, is somewhat misleading since it does not invariably follow that such tremor rises in almost a straight line. Some of the patients remain partially or fully controlled by medication for years, but for many of them the course is bitter and the tremor rises progressively into severest proportions.

RESULTS OF TREATMENT

The results of treatment among the 520 tremor cases are summarized in table 3. They represent the favorable and unfavorable sides to the story. The table shows 68 per cent successes for minor tremor, as compared with only 24 per cent for major tremor. It is obviously a sad commentary on our advances in therapy, when three fourths of the cases suffering with severe tremor obtain not a trace of relief from all current remedies. The story is even more clearly depicted in figure 2, where the high ratio of successes in the minor forms of tremor stand out in graphic contrast to the high ratio of failures in major tremor.

Returning to table 3, it will be noted that cases in whom tremor is unchanged or stationary account for 13 per cent of the series and those in whom

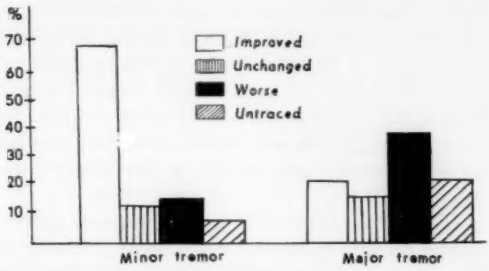

FIG. 2. The results of treatment in 520 cases of tremor.

tremor becomes progressively worse compose another 20 per cent of the cases. The 11 per cent of untraced cases represents chiefly patients who became discouraged by the lack of results from treatment, especially the aged cases, and drifted elsewhere. Rightfully, such cases should be counted among the failures, since it is almost axiomatic that patients who derive satisfaction from their treatment rarely present difficulties in tracing.

In table 4 rough estimates are provided with regard to the comparative value of the various compounds currently employed against tremor. Since this is not a controlled study but rather a survey, it is not possible to equate the efficacy of the various preparations in terms of similar samplings, duration of treatment, and the like. An attempt is made to present an evaluation based on clinical observations.

It is our impression that hyoscine is the mainstay against tremor and, if well tolerated, produces highly gratifying results even in patients with the most severe tremor. Benadryl is likewise helpful against all types of tremor, but its good effects wear off after a short while and many patients cannot tolerate the drug. Stramonium affords reasonably favorable results and the older patients accept it in the graded dosage of drops better than in pill form.

TABLE 4

MERITS OF DRUGS CURRENTLY EMPLOYED TO OVERCOME TREMOR

Nature of Drug	*Effects in Minor tremor*	*Effects in Major tremor*
Hyoscine	+++	++
Benadryl	++	+
Stramonium	+	±
Artane	+	±
Thephorin	+	?
Rabellon	±	0
Bellabulgara	±	0
Vinobel	±	0
Tolserol	±	0
Panparnit	?	0
Genoscopolamine	0	0

Artane has been found of value in many cases of minor tremor, but is not effective in the major variety, except in isolated instances such as case 2. Theporin is of decided benefit to some cases of minor tremor. Rabellon, Vinobel, Bellabulgara, Panparnit and Tolserol provide occasional relief in mild tremor, but are of limited or no value in major types of tremor. Genoscopolamine seemingly has no greater value than a placebo. The details of administration, dosage, and actions of the above listed drugs are available elsewhere.[10–12]

Thus, it is observed that mild forms of tremor present only a minor problem as regards treatment, since there is a wide assortment of effective remedies for cases of minor tremor.[13] Furthermore, since mild tremors are readily controlled by a minimum of medication, there is rarely occasion to increase the dosage to levels which are accompanied by disturbing side-reactions.

The major form of tremor, on the other hand, presents a most challenging problem. Here, the tremor persists throughout the day and the continuous activity of head, arms and legs causes patients to lose weight, become emaciated and feel weak. Their predicament is further aggravated by the fact that the annoying tremor does not permit them a moment of relaxation or peace of mind, so that the ensuing nervousness reacts badly upon the autonomic and somatic nervous system. There is constant sweating and a loss of appetite, at a time when they can ill afford to lose calories. They find it difficult to fall asleep. There are fits of crying, self-pity and depression as they view the future with despair and utter helplessness. There is progressive loss of interest in food, surroundings and life itself, so that it should hardly be surprising that there is an occasional attempt at suicide among them. Some terminate in state hospitals because of lack of better facilities for them. It is thus of tremendous import, that 25 per cent of parkinsonism patients suffer from the major form of tremor and that the vast majority of them become progressively worse, under any and all forms of current therapy.

REPORT ON RESULTS OF NEW COMPOUNDS

While there are reasonably good remedies against rigidity, it has been shown here that physicians are far less equipped to meet the challenge presented by the major form of tremor. Hope rises nevertheless from the fact that pharmacologists have become alerted to the problem and are synthesizing new drugs to meet the situation. Herein is presented a report on experience with one new compound, tropine benzohydryl ether methane sulfonate, or MK-02, which has been used for over a year. It is a synthetic preparation that combines the active radicles of atropine and Benadryl. Details regarding dosage, side-reactions and effects upon rigidity, contracture and muscle spasm are available in the literature.[14] This report will be chiefly concerned with the effect of MK-02 in patients with severe degrees of tremor.

Table 5 summarizes the results of treatment with MK-02 in 40 of the 102 patients who had failed to improve with hyoscine, Benadryl and other stand-

TABLE 5

TREATMENT OF 40 MAJOR TREMOR CASES WITH TROPINE BENZOHYDRYL ETHER (MK-02)

Result of Treament	*Total* No.	*Per cent*	*Arteriosclerotic cases*	*Idiopathic cases*	*Postencephalitic cases*
Improved	15	38	8	3	4
Unchanged	12	30	6	4	2
Worse	13	32	11	2	0
Total	40	100	25	9	6

ard drugs. The discovery that 38 per cent of these cases obtained relief from tremor came as a surprise to the present investigators.

Of particular interest is that MK-02 was well tolerated even by the elderly patients who were unable to take but small doses of the other drugs. A description of several cases may bring its effects into clearer perspective, than could be gained from numbers in a table.

Case 3.—A 51 year old male with idiopathic parkinsonism suffered tremor and rigidity of the left side of the body for two years. Bellabulgara caused disturbing side reactions. Artane treatment was started in October 1949 and had a favorable action for a time, but the effects wore off and the tremor spread to the other side. The patient had to give up employment and was greatly depressed. MK-02, 1 mg. twice daily, was added to Artane on January 10, 1951, and he felt freer in body but remained disgruntled over domestic and unemployment problems and the dryness of the mouth caused by MK-02. Upon discontinuing the drug two months later, his shaking became worse and he was hardly able to get about. On May 5, 1951, he returned to MK-02 and obtained immediate relief. On June 7 he ran out of medicine and within several days re-experienced severe rigidity and tremor. After resuming MK-02 he reported the following: "I was like a changed man with the new medicine – before that my arms were so stiff and weak that I could not cover my body with the blankets during the night. When I became uncovered I felt chilled, restless, sweaty and could not lie in one position for more than an hour. With MK-02 I was able to move easier and could cover myself; I felt relaxed and slept right through the night, and in the morning I was rested and had a good feeling in the body that lasted all day. With the new medicine I can do work around my house, without it I can do nothing." He has continued in favorable condition on MK-02 and Artane.

Case 4.—A 59 year old patient with arteriosclerotic parkinsonism has had advanced tremor and rigidity of the extremities for the past four years. Artane alone failed to control the tremor although it helped in other ways. In April 1951, MK-02 was added. His wife reported a marked change for the better: "Before, my husband would get out of bed ten times a night because he was tense, restless and shaking – now he sleeps right through the night. Before, he avoided people because it took him so long to say a few words and he had to shift his position every few minutes. Now he talks and smiles so easily that he looks for company; he is calm in mind and the tremor is gone. He can sit and read a paper for hours at a time." The patient has continued his improved status on 2 mg. of Artane and 1 mg. of MK-02 three times a day.

Case 5.—A 72 year old patient had advanced arteriosclerotic parkinsonism, which began in 1941 with tremor and rigidity on the left side and spread to the neck, trunk and the right side. Artane was started in September 1949 and later Bellaburgara was added. The latter caused too much dryness and had to be discontinued. He fared better with Artane alone, but its effect wore off so that in time the dose had to be increased to 5 mg. three times daily. Following an abdominal operation for adhesions in 1951,

he became very tremulous, depressed and insomniac. Hyoscine and Medinal were added, but the tremor continued to get steadily worse and he was unable to sleep. In April 1952, 2 mg. of MK-02 were added at bedtime. Two months later his wife reported marvelous improvement. She stated that the patient became relaxed the first night of medication; that his tremor disappeared and that he slept better than at any time in the previous three years. She also reported that since taking the new drug he found no further need for hyoscine and Medinal. Of added interest is its cumulative action. When he ran out of MK-02 for two days he continued to sleep well and to feel relaxed.

Although the results obtained from the use of MK-02 in patients with severe tremor have proved highly gratifying, one cannot lose sight of the 62 per cent of cases that were not helped by the drug at all. Nevertheless, the fact that a new synthetic can bring decided relief to a number of patients who were not benefitted by current remedies holds promise that more effective compounds may be found. Several other new drugs are being investigated at this time but none has been sufficiently tested for an expression of results.

SUMMARY

1. Tremor of a minor or major form was found in 520 out of 544 cases of parkinsonism.

2. The results with remedies in current use show that 68 per cent of patients with minor tremor are benefitted, as against only 24 per cent of patients with major tremor. Reasons for the failure of medication against severe tremor are offered and the need for new and better drugs is emphasized.

3. Preliminary data are submitted with regard to treatment with MK-02 in 40 cases of severe tremor that had failed with all current remedies. With the use of this new synthetic, 38 per cent of the tremor cases showed decided improvement. Thereby hope is engendered that ultimatly a compound may be synthesized that will control tremor in even the most severe cases.

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Total Protein Content of Cerebrospinal Fluid in Multiple Myeloma

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DEGENHARDT AND SHEEHAN[1] found an increase in the total protein content of the cerebrospinal fluid in six of 11 patients with multiple myeloma. Although it is presumed that there was no block on manometric studies, this was not clearly indicated. In their case 11, it is noted that there was "complete compression and complete paraplegia at D9-L1." No neurologic symptoms were present in their other ten cases, except in case 4 in which pain radiated down the right leg. Degenhardt and Sheehan suggested that the spinal fluid protein may increase before any changes can be detected in the protein value of the serum. Cabot[2] reported a protein content of 95 mg. per 100 cc. in a patient with multiple myeloma; however, tumors were extending into the subarachnoid space. Kabat, Freedman, Murphy and Knaub[3] found total protein concentrations to be 15 mg. and 33 mg. per 100 cc. in two cases of multiple myeloma.

The total protein concentration in the spinal fluids of 21 cases of multiple myeloma have been studied. Each patient had manometric tests performed with a sphygmomanometer cuff set at varying pressures in order to determine the presence or absence of block. In several patients contrast media were employed. Results of the several tests performed are summarized in table I. The diagnosis of multiple myeloma was confirmed by examination of bone marrow, biopsy, or examination of tumors removed at operation.

In this series, three patients had subarachnoid block demonstrated by contrast media, one complete and two partial. The patient with complete block (case 19) had a paraplegia with a sensory level at D7; one of the patients with partial block (case 20) had a flaccid paraplegia with a sensory level at D8; and the other patient (case 21) with partial block had a cauda equina syndrome. In the other cases, the possibility of a small tumor encroaching upon the subarachnoid space could not be absolutely excluded by manometric tests. However, Pantopaque myelography was performed in case 15 in which the patient had an elevated spinal fluid protein of 100 and 83 mg. per 100 cc.

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TABLE 1

Case No.	Age	Sex	Race	Onset of Symptoms	Symptoms and signs	Diagnosis x-ray	Confirmed by bone marrow	G. per 100 cc. Serum protein Total	alb.	globulin	Bence-Jones Urine	C.S.F.	mg. per 100 cc. Total C.S.F. Protein	Manometrics	Comment
1	59	F	C	4 mo.	weakness of limbs	skull	+	6.3	4.4	1.9	+	O	57	no block	died
2	70	M	W	3 mo.	weakness - no neurologic signs	skull, humeri, radii, ulnae	+	9.9 7.7 7.0	3.4 3.1 3.5	6.5 4.6 3.5	O O	 +	54 44 34	no block 28 days later no block 17 days later no block	16 lymphocytes 5 lymphocytes died
3	50	M	W	2 mo.	pain in chest, weakness, no neurologic signs	spine, ribs	+	7.1	3.4	3.7	+	O	45	no block	discharged
4	62	M	W	1 yr.	pain in back, shoulder, no neurologic signs	skull, pelvis, ribs, sternum	+	7.34	4.41	1.5	O		58	no block	died
5	68	F	W	4 mo.	headaches, nodules in skin, right eye proptosed, nuchal rigidity, coma	skull, humerus, sternum	+	7.8	4.2	3.6			58	no block	died
6	53	M	W	8 mo.	paresthesiae in fingers and toes, weakness of extremities, arreflexia, signs of peripheral neuropathy	0	+	6.7	4.9	1.4	+		212	no block	died
7	67	M	W	3 mo.	pain in back, shoulders, no neurologic signs	skull, ribs, spine	+	8.5	2.6	5.9	O		31	no block	died
8	58	M	W	1 yr.	pain in shoulder, wasting of limbs, signs of peripheral neuropathy	ribs, skull, shoulder girdle	+	6.2	3.9	2.3	+		71	no block	died amyloid of tongue
9	34	F	W	4 yr.	back pain, no neurologic signs	ribs, spine femur	+	10.2	2.9	7.3	O		29	no block	discharged
10	53	M	C	8 mo.	nodules on body, peripheral neuropathy	0	+	6.33	3.3	3.0	O		72	no block	died
11	48	M	W	15 mo.	pain in back, no neurologic signs	spine, skull, pelvis	+	6.8	3.0	1.8	+		48	no block	discharged
12	69	F	W	18 mo.	pain in back	spine, skull, ribs	+	7.3	2.9	4.4	O		22.8	no block	discharged
13	57	M	W	9 mo.	pain in chest, then all bones, no neurologic signs	skull, ribs, spine	+	11.3	2.5	8.8	O		50	no block	died
14	59	F	W	24 mo.	pain in arms, numbness right hand, atrophy of small muscles right hand, sensory changes of peripheral neuropathy	clavicle	+	6.54	4.12	2.42	+		31	no block	died generalized amyloidosis
15	61	M	C	"several months"	pain in neck, no neurologic signs	spine, skull, clavicle	+	11.5	3.7	7.8	O	O	100 83	no block, myelography negative	died
16	56	M	W	14 mo.	bone pain, no neurologic signs	all bones	+	6.56	3.89	2.67	O	O	44	no block	discharged
17	65	F	W	8 mo.	bone pain, no neurologic signs	skull	+	7.6	4.8	2.8	+	O	23	no block	died
18	47	F	C	11 mo.	swelling left mandible	spine, clavicle	+	8.98	3.82	5.16	+	O	50	no block	in hospital
19	66	M	W	5 wks.	pain in back, paraplegia, sensory level at D7	spine					O		559	block on manometrics and lipoidal at D7, operated—extradural myeloma	died
20	40	M	W	2 mo.	pain in back, flaccid paraplegia, sensory level at D8	spine					O		195 45	6 lymphocytes, partial block operated, myeloma removed; 4 weeks previously, air myelography negative	died
21	59	M	W	6 mo.	pain in back, cauda equina syndrome	pelvis, femur, spine	+	10.2 9.8	3.9 3.6	6.3 6.2	O O	 ±	75 93	myelography constant filling defect at L3	died

on two occasions without any neurologic signs and with no block on manometric tests; no deformity was demonstrated.

If the three patients with evidence of block are excluded, then ten patients had spinal fluid protein values of 50 mg. or more per 100 cc. and eight were below 50 mg. per 100 cc. The highest total protein concentration without the presence of block was 212 mg. per 100 cc.

Alterations in the protein concentrations of the serum in multiple myeloma have been found both by chemical and electrophoretic methods.[4–12] Alterations in the protein pattern of the spinal fluid of multiple myeloma cases have been demonstrated by Kabat, Freedman, Murphy and Knaub[3] and by Labhart, Schweizer and Staub[13] by electrophoretic methods. In the present study an attempt was made to determine whether the total protein content of the cerebrospinal fluid is increased in multiple myeloma and if so, whether neurologic findings are necessarily present to account for this increase. The results show that an increased protein value of the spinal fluid may occur in the absence of neurologic signs, even including normal contrast media studies.

TABLE 2

No. of cases	*Cerebrospinal fluid protein, mg. per 100 cc.*	*Serum protein, gram per 100 cc.*
5	50 or over	7.5 or over
4	50 or over	Below 7.5
3	Below 50	7.5 or over
6	Below 50	Below 7.5

To determine whether there is a relationship between the total spinal fluid and total serum protein concentrations, serum proteins were drawn at the same time as the spinal punctures were performed in 20 cases of the series.

If 7.5 grams or more per 100 cc. is considered as signifying an increase in the total serum protein,[4] then nine of 19 of the cases showed an elevated serum protein. Table 2 shows the relationship between the total spinal fluid and serum proteins in the series.

Although there is a suggestion of a possible relationship between the total spinal fluid and the total serum protein, as illustrated by case 2 in which the spinal fluid protein decreased with a diminution of the serum protein, and by the increase of spinal fluid protein to 100 mg. per 100 cc. in case 15 with the highest serum protein of 11.5 grams per 100 cc., there is no consistent relationship between the spinal and serum protein values. Table 2 shows that five of eight patients with elevated serum proteins had elevated total spinal fluid proteins, and four of ten patients with serum proteins below 7.5 grams per 100 cc. had spinal fluid proteins of 50 mg. or more per 100 cc. It is interesting to note that the highest spinal fluid protein value was 212 mg. per 100 cc. in a patient (case 6) with a picture of peripheral neuropathy. In three other patients (cases 8, 10 and 14) with a similar clinical syndrome of periph-

eral neuropathy, the spinal fluid proteins were 71, 72 and 31 mg. per 100 cc. respectively. There is a possibility that peripheral neuropathy in itself may elevate the spinal fluid protein, as it does in diabetic peripheral neuropathy.[14] However, the spinal fluid protein was normal in a case of peripheral neuropathy with multiple myeloma reported by Kurnick and Yohalem.[15] Our results indicate that there is no consistent relationship between the total spinal fluid and total serum protein values.

Another possible explanation for the increase in the spinal fluid protein in multiple myeloma may be an alteration in the permeability of the choroid plexus barrier, as has been invoked to account for the elevated spinal fluid protein in myxedema[16] and in chronic nephritis.[17] However, Kabat, Moore and Landow,[18] by electrophoretic studies of spinal fluids in neurosyphilis, indicated that the per cent of globulin may be higher in the cerebrospinal fluid than in the blood and their data suggested that some formation of gamma globulin could take place in the tissues of the central nervous system and then be passed into the spinal fluid. They objected to the hypothesis of altered permeability of the hematoencephalic barrier in producing the increase in globulin since there is no similar or greater per cent increase in the smaller albumin molecule as would be expected. In multiple myeloma the globulin fraction of the spinal fluid is raised more than the albumin, as demonstrated by electrophoretic methods,[13] and the possibility exists that some of the increase in protein may be produced by the central nervous tissues and passed into the spinal fluid. It is possible that a substance elaborated by the myeloma cell, even when situated outside the nervous system, may act as the agent in causing the increase of protein in the cerebrospinal fluid. Scheinker[19] was of the opinion that the neurologic complication in his case of multiple myeloma was due to a toxin, perhaps the Bence-Jones protein, produced by the myeloma cell. The present results indicate no definite relationship between the presence of Bence-Jones protein and an increase in the total protein of the cerebrospinal fluid. Of 17 cases in which Bence-Jones protein was tested in the urine, four had Bence-Jones protein with an increase of total spinal fluid protein, four had Bence-Jones protein with normal total spinal fluid protein, four with negative Bence-Jones protein in urine had an increase in the total spinal fluid protein, and five with negative Bence-Jones protein in urine had normal total spinal fluid protein.

From the present data one cannot state that an increase in the protein content of the cerebrospinal fluid may be the first manifestation of multiple myeloma, since only verified cases were studied. To prove such a possibility, a series of patients with increase of cerebrospinal fluid protein for which no causes are available would have to be followed for several years.

Table 1 also shows several other interesting findings in the series of multiple myeloma. Two cases had an increase of cells in the cerebrospinal fluid; case 2 had 16 lymphocytes and case 20 had six lymphocytes. The highest cell count in Degenhardt and Sheehan's[1] series was three lymphocytes. Bence-

Jones protein was found in the urine of eight of 20 cases in the present series. This is less than the incidence of 65 per cent reported by Copeland and Geshickter;[20] it is closer to the 47 per cent reported by Adams, Alling and Lawrence.[11] Only one positive and one doubtful Bence-Jones test was found in eight cases in which it was tested for in the cerebrospinal fluid. Positive Bence-Jones tests on the spinal fluid were demonstrated in the cases of Magnus-Levy[21] and Müller.[22] Degenhardt and Sheehan[1] were unable to elicit a positive reaction in the three cases tested.

SUMMARY AND CONCLUSIONS

1. Determination of the total spinal fluid protein was performed in 21 patients with multiple myeloma. Total serum protein estimations on blood drawn at the same time as the lumbar puncture were done in 20 of the patients.

2. Excluding the three patients with manometric block, ten patients had spinal fluid protein values of 50 mg. or more per 100 cc. and eight were below 50 mg. per 100 cc.

3. No relationship could be demonstrated between the total serum and total spinal fluid protein concentrations.

4. No relationship could be demonstrated between the presence or absence of Bence-Jones protein in the urine and the total spinal fluid concentrations.

5. The reason for the elevation in the protein content of the cerebrospinal fluid in multiple myeloma is not known. Possibly it is due to an alteration in the permeability of the choroid plexus, or perhaps it is due to an increase in production, especially of globulin, by the central nervous tissues, with subsequent passage into the spinal fluid.

6. There was no correlation between an elevated total protein in the cerebrospinal fluid and signs or symptoms or involvement of the nervous system. Hence, an elevated total protein in the cerebrospinal fluid does not necessarily signify the presence of neurologic complications; in such instances the increase of protein in the spinal fluid is probably a general manifestation of the disease.

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Intellectual strain as well as bodily exertion may prove an exciting cause of megrim, and studious and literary as well as professional persons should exercise caution in this respect; but as far as my experience goes it is far more frequently accessory to the general malady in the manner I have already explained than a provocative of the seizures.

Lastly, the following passage from Dr. Salter's work on the treatment of Asthma, is scarcely less applicable to the case of some habitual sufferers from megrim. "There is one general rule," he says, "which, trifling as it may seem, is perhaps exceeded in importance by none, and by attending to which the asthmatic may do more to evade his attacks than by any other. It is, to establish a *rigorous uniformity of life*, to make one day the exact counterpart of another, and to avoid irregularities of every kind. Asthma often seems as if it were lying in ambush watching its opportunity, or on the look out for some loophole through which to make its attack, and there is hardly any change of life or habit of which it will not, as it were, take advantage – change of air, change of sleeping apartment, alteration of meal hours. I have already referred to this subject in speaking of the tendency to habitude which characterizes asthma; and I would only now enforce the great importance of the asthmatic guarding himself from all sources of offense by tying himself down to a life of monotonous regularity."

Edward Liveling in *On Megrim, Sick-Headache, and Some Allied Disorders*, published in 1873.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Robert Ebert, M.D., Sidney Schulman, M.D. and Richard B. Richter, M.D.

PRESENTATION OF CASE

A 56 year old white female was admitted to the medical service of the University of Chicago Clinics on June 3, 1952. She was unable to give a coherent story of her illness and complained only of difficulty in controlling motion of her left hand. According to a friend, the patient had seemed normal until a few days prior to admission. She then developed a staggering gait, falling several times, and appeared disoriented except for occasional lucid moments.

The patient was first seen in the dermatology clinic at the University of Chicago in November 1951, because of severe moniliasis of the mouth, hands, feet, ears and perineum. This skin affliction had begun in October of 1948 and had been resistant to all treatment. She was followed in the dermatology out-patient department where C. albicans was repeatedly cultured from the skin lesions, but various therapeutic regimens were of no avail. In February 1952 an abscess developed at the angle of the left jaw, and the patient developed a spiking fever and malaise. She was admitted on the ear, nose and throat service on February 28, 1952 and the abscess was incised and drained on March 13, 1952. Tubercle bacilli were found in great numbers in the pus from the abscess, and cultures and guinea pig inoculations were positive for mycobacterium tuberculosis. An x-ray of the chest was essentially negative. She was given 1 gm. streptomycin every other day and 8 gm. PAS daily. On this regimen her temperature returned to normal, the abscess decreased in size and drainage decreased. She was discharged from the hospital on April 8, 1952 and was told to continue daily PAS and to return to the out-patient department once a week for a gram of streptomycin. Slow improvement of the tuberculous abscess continued on this regimen.

The past history was non-contributory except for the illness noted above.

General physical examination revealed a well-developed obese white female who was disoriented and drowsy. The temperature was 38.4° C., pulse 80, respiration 22 and blood pressure 144/80. Widespread scaling erythematous lesions were present over the fingers, feet, perineum, and beneath the breasts. Finger nails and toenails were almost completely destroyed. Superficial ulcerations were present on the mucous membranes of the mouth. A draining sinus was present at the angle of the left jaw but there was little swelling in this area. Aside from an apical systolic murmur the general physical examination was otherwise negative.

Laboratory examination showed a white blood count of 6,250, with a normal differential count, 13.5 grams of hemoglobin

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per 100 ml., a red blood count of 4.06 million, a negative urine except for rare granular and hyaline casts, and a sedimentation rate of 21 mm./hr. by the Cutler method. A lumbar puncture the day of admission showed an initial pressure of 260 mm. of water with a final pressure of 140 mm. of water after removing 12 cc. of turbid fluid. The cell count was 320 and all cells were mononuclears. The Pandy test was one plus, total protein 220 mg. per cent, sugar 20 mg. per cent, chlorides 109 mM/L, Wassermann negative, colloidal gold 00123-32110, and acid fast bacilli were found with ease in the spun sediment. Cultures and guinea pig inoculation of spinal fluid were positive for tubercle bacilli.

Clinical course: The patient was started immediately on isoniazid, 200 mg. daily, and 2 gm. of dihydrostreptomycin daily. In addition she was given 50 mg. of streptomycin intrathecally every other day from June 4, 1952 to June 14, 1952 and every third day thereafter. Initially the patient appeared to improve. Her fever subsided by the fourth hospital day and she seemed more alert than on admission. The spinal fluid was clear by June 20, 1952, the cell count was 88 and the Pandy test negative. The pressure remained somewhat high at 250. Except for rare lucid moments, however, the patient remained disoriented for time and place during her entire illness. She was incontinent of urine and feces much of this time.

On June 22, 1953 she became exceedingly belligerent and difficult to control. She threw her food at the attendants and spit at them when they approached her bed. She refused her medication and was sedated only with great difficulty.

On June 23, 1952 she appeared comatose and unresponsive. Because the patient was unable to take oral medication, 300 mg. of isoniazid daily was given intramuscularly beginning June 23, 1952. The patient gradually became more deeply comatose, and on June 24 her temperature rose to 40.5° C., her pulse rate increased, and moist rales could be heard over both lung fields posteriorly. Penicillin was started but the high fever and rapid pulse rate continued; her respiration became labored and she expired on June 26, 1952.

CLINICAL DISCUSSION

DR. EBERT: In looking back over this patient's history I am impressed by the number of unusual problems which she presented. To begin with she had an unusually resistant generalized monilia infection which had been present since 1948. When she developed a mass in the neck which became fluctuant, it was naturally assumed that this was a complication of the moniliasis. The discovery of tubercle bacilli on smear of the pus from the abscess was quite unexpected.

The initial response to specific therapy of the tuberculosis seemed to be favorable. Fever subsided about ten days after starting streptomycin and PAS, the patient felt better, and drainage from the abscess diminished. After discharge from the hospital slow improvement in the neck abscess continued.

The development of signs and symptoms of tuberculous meningitis came as a complete surprise. Clinically she had done well till five days before her second admission, and she had been on continuous chemotherapy. The dosage of streptomycin was small but she had been receiving PAS daily, and the amount of chemotherapy had been sufficient to control the local tuberculous lesion in the neck.

At the time of her second hospital admission the initial clinical response to chemotherapy once again seemed favorable. Shortly after beginning isoniazid and increased amounts of streptomycin the patient became more alert, her fever subsided and the spinal fluid findings reflected the improvement. On more vigorous chemotherapy the draining sinus at the angle of the jaw closed completely and there was only slight induration in the region of the neck abscess.

The deterioration in her mental condition on the nineteenth hospital day was unexpected and difficult to understand in view of the maintained improvement in the spinal fluid findings. Since the patient had displayed lack of resistance

to tuberculous infection in the past, it was assumed that a new tuberculous focus had developed within the brain and isoniazid was increased to 300 mg. daily. Her condition continued to deteriorate, however, and on the twenty-second hospital day her temperature rose to 40.5 C. and moist rales could be heard throughout both lung fields posteriorly.

The cause of death was interpreted as an overwhelming tuberculous infection of brain and meninges complicated by a terminal bronchopneumonia.

NEUROLOGIC DISCUSSION

DR. SCHULMAN: I saw this patient on her third day in the hospital. At that time she was quite stuporous, but could be aroused sufficiently to speak and carry out simple commands. She was oriented in time and place, and on the whole understood what was said to her, but her replies to questions about her symptoms were delayed, slow and vague. She denied headache and said that her only trouble was weakness in the left arm. Her speech was somewhat thick and slurred, but not nasal. Responses to spoken commands, such as "put out your tongue" and "raise your hands above your head" were also delayed and slow, and they were often associated with much irregular, adventitious movement. It was obvious that there was an independent, gross wavering ataxia and dysmetria in the voluntary movements of the left arm and left leg. There were no athetoid movements, however. Pin prick stimuli appeared to be less well appreciated over the entire left upper extremity than elsewhere, but further sensory examination was impossible because of her mental state. There was no lateralized weakness, and the deep reflexes were symmetrical and generally hypo-active. The abdominal reflexes could not be obtained. The plantar responses were quite inactive, and what movements were seen were equivocal. The optic disks were normal and remained so throughout her course. The visual fields were grossly full, and the remaining cranial nerves were also normal. There was slight nuchal rigidity, but none of the other signs of meningeal irritation.

From the spinal fluid findings alone, of course, it was obvious that this patient had tuberculous meningitis, and her symptoms of general cerebral dysfunction could be explained quite satisfactorily on this basis. But the ataxia of the left arm and leg and the sensory defect in the left arm pointed to a focal cerebral lesion on the right side, probably in the thalamus. It was my impression that this could well have been either an infarction from tuberculous vasculitis of a deep cerebral artery, or a tuberculoma which had perhaps also been the source of the meningitis.

After the initial period of improvement, her subsequent course under treatment proved to be much more difficult to explain because of the progressive clinical deterioration with increasing confusion, disorientation, and finally coma and death in spite of the continuing improvement in the spinal fluid findings. There was no evidence of increasing intracranial pressure, which might have resulted from a tuberculoma acting as an expanding lesion, or from obstruction of cerebrospinal fluid pathways by a fibrotic or exudative process in the meninges of the basal cisterns. For this reason, the most plausible explanation at the time seemed to be a progressive and extensive bilateral, deep cerebral infarction from tuberculous arteritis of the vessels at the base of the brain.

There is, however, another possible factor in this patient's fatal outcome, which perhaps should have been suggested to us by her paradoxical course, but which was in fact not considered at all at the time of her terminal illness. Since that time, reports have appeared in the

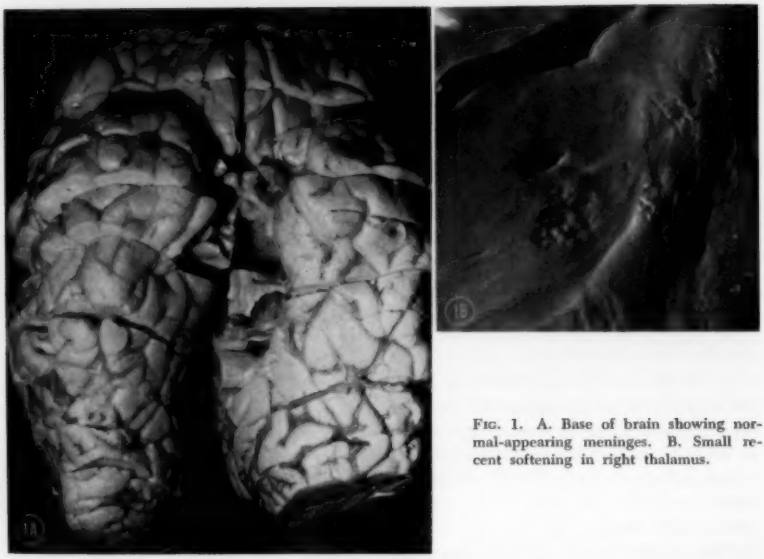

FIG. 1. A. Base of brain showing normal-appearing meninges. B. Small recent softening in right thalamus.

literature and others have been received by the American Trudeau Society indicating that the nicotinic acid derivatives are toxic to some patients in the dosage ordinarily used, and that the nervous system bears the brunt of this toxicity. It is possible that this may have been an important factor in the decline of Dr. Ebert's patient. It is true that the reported toxic manifestations from the nicotinic acid derivatives have generally been mild, the most common signs being restlessness, insomnia, involuntary muscular twitching and hyperactive reflexes. Furthermore, they have often been transitory, even when treatment is continued. On the other hand, there have been a few patients in whom convulsive seizures have appeared, and others with major psychotic reactions, one of them showing rather severe residual organic cerebral impairment.

I believe that these observations, taken together with the clinical course in Dr. Ebert's patient, suggest strongly that isoniazid intoxication may have played an important role in her fatal outcome. If this interpretation is correct, a question of some importance is raised in regard to the treatment of tuberculous meningitis with the nicotinic acid compounds, for it is conceivable that situations may arise in which it would be extremely difficult to decide whether advancing neurologic symptoms were from the disease or the treatment.

PATHOLOGIC DISCUSSION

DR. RICHTER: In the general pathologic examination there was no extensive or active involvement of any of the organs by tuberculosis, and none in the hilar lymph nodes or the lungs. Recent non-tuberculous bronchopneumonia was found in both lower lobes. In the fibrous mass from the region of the draining sinus in the neck, there were dense layers of fibrous tissue containing a few

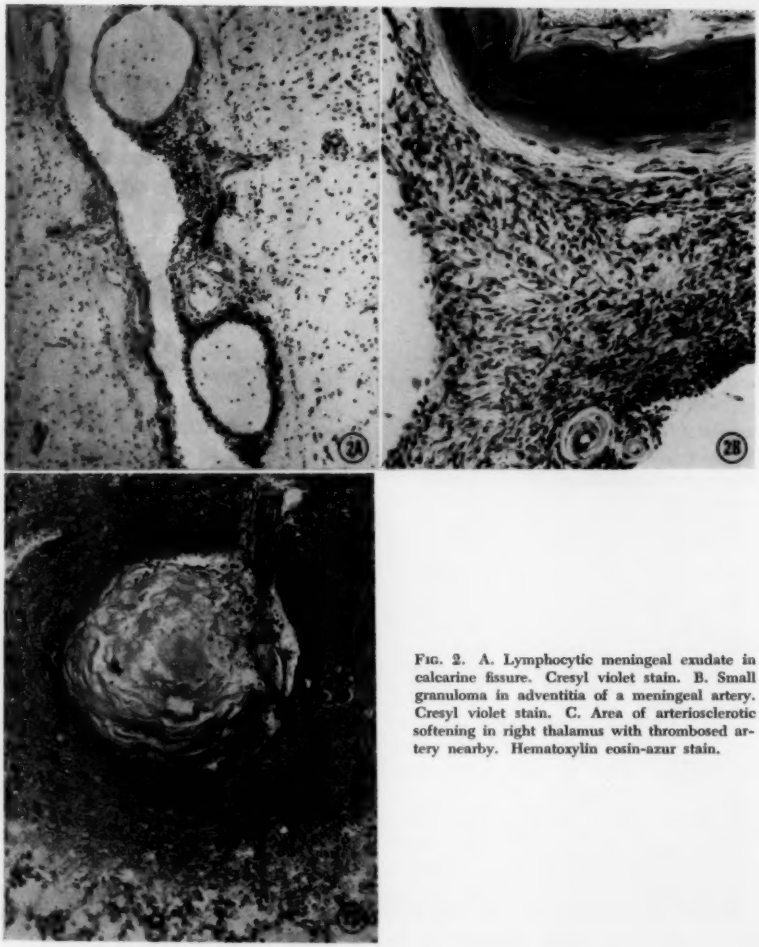

FIG. 2. A. Lymphocytic meningeal exudate in calcarine fissure. Cresyl violet stain. B. Small granuloma in adventitia of a meningeal artery. Cresyl violet stain. C. Area of arteriosclerotic softening in right thalamus with thrombosed artery nearby. Hematoxylin eosin-azur stain.

residual lymphocytes and some reticular macrophages and fibroblasts, but nothing remained that was diagnostic of tuberculosis in hematoxylin-eosin stains.

The leptomeninges of the base of the brain and over the convexity were thin and transparent without evidence of exudate or fibrous thickening in any place, nor were any tubercles visible. The arteries at the base of the brain were rigid, thick-walled and contained numerous atheromatous plaques. The external appearance of the cerebral hemispheres was quite normal with no indication of edema. In serial coronal sections through the cerebral hemispheres and through

the cerebellum and brain stem, the only abnormality observed was an oval area of softening, 0.6 cm. in greatest dimension, in the posterior ventral portion of the right thalamus. The ventricles were only slightly larger than is usually seen in a patient this age; the ependyma was smooth. From the appearance of the gross specimen it could only be said that the tuberculous meningitis, demonstrated clinically, had healed completely and the only diagnosis that could be made was advanced atherosclerosis with recent infarction in the right thalamus.

The microscopic examination, however, disclosed that the situation was quite otherwise. Everywhere in the subarachnoid spaces there were diffuse infiltrations, mild to moderate in degree, often composed only of lymphocytes or at times of lymphocytes and a few histiocytes. Such cellular infiltrations were very sparse in the pia-arachnoid of the frontal and parietal lobes, more intense over the occipital and temporal lobes, especially in the deeper sulci, and around the pons and upper cervical cord. In all of these locations, with one exception, the inflammatory process was that of diffuse non-specific meningitis and had not proceeded to granuloma formation in the form either of tubercles or more extended granulations. Nor did the meningeal vessels display in their walls the infiltration, proliferation or degenerative changes characteristic of tuberculous vasculitis except for one rather large artery at the base, beneath the left hippocampal gyrus, which contained in its adventitia a small discrete tubercle made up of masses of lymphocytes and a few histiocytes scattered among many proliferating fibroblasts. Almost all of the pial arteries, however, showed the medial thickening and hyalin change of advanced arteriolar sclerosis. In Ziehl-Neelsen stains there were occasional tubercle bacilli where the leptomeningeal lymphocytic infiltrations were most intense; within the single tubercle they were present in great profusion.

Beneath regions of more intense meningitis, there was a mild reaction of astrocytes and microglia in the molecular layer of the cortex, but this was much less than is usually seen in tuberculous meningitis and there was no marginal encephalitis. The most remarkable parenchymal lesion encountered was a small inflammatory focus in the dorsal part of the ventral lateral nucleus of the left thalamus composed of sheets and masses of lymphocytes, together with a few histiocytes. Within the area were some hypertrophic astrocytes and degenerating neurons, but no giant cells or caseation and virtually no proliferation of connective tissue or blood vessels within or around the focus. Several veins in the region had heavy perivascular cuffs of lymphocytes without granulomatous reaction in their walls. The area was teeming with tubercle bacilli. While the lesion was discrete, it did not have as compact or circumscribed an appearance as the usual miliary tubercle and was interpreted as a focus of subacute tuberculous encephalitis.

The lesion seen grossly in the right thalamus was obviously an ordinary softening occupied by large numbers of compound granular cells. There was no associated inflammatory reaction and no tubercle bacilli were seen. In close relation to the lesion was a small artery occluded by an organized thrombus. There was no evidence of inflammation in the walls of this vessel or of others in the vicinity.

The neurons throughout the cortex had an appearance of moderate degeneration in the form of chromatolysis, swelling of the cytoplasm and increased visibility of dendrites. Such changes were present equally in all parts of the cortex and in all cortical laminae. They were seen also in the neurons of the thalamus and in the pons including those of

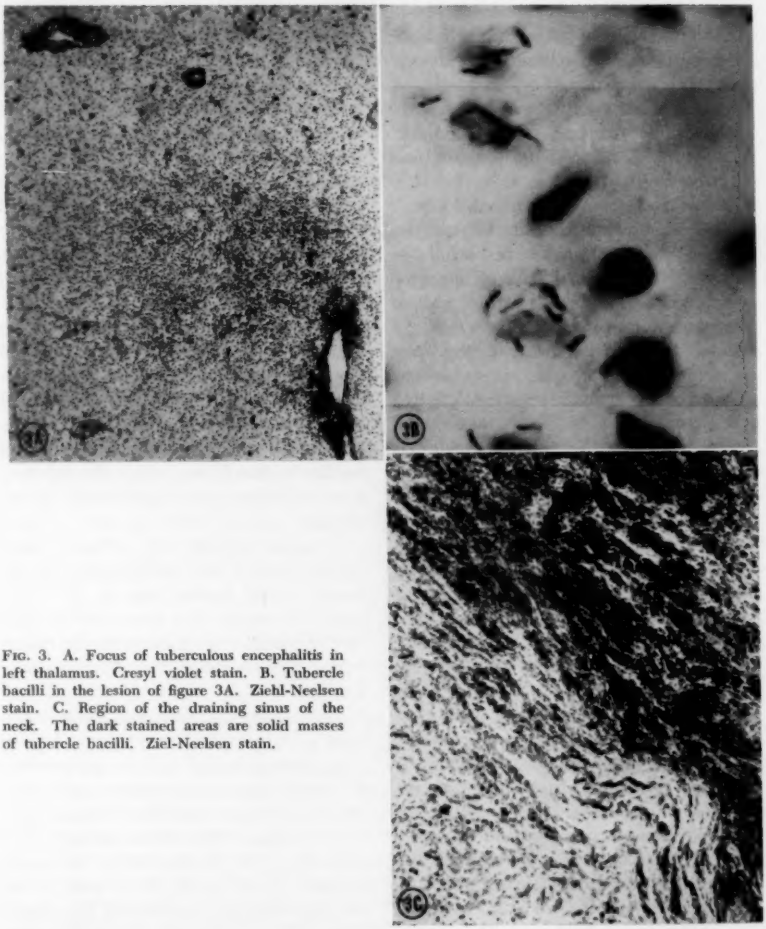

FIG. 3. A. Focus of tuberculous encephalitis in left thalamus. Cresyl violet stain. B. Tubercle bacilli in the lesion of figure 3A. Ziehl-Neelsen stain. C. Region of the draining sinus of the neck. The dark stained areas are solid masses of tubercle bacilli. Ziel-Neelsen stain.

the abducens and facial nuclei, but not in the Purkinje cells or the neurons of the anterior horns.

Interpreting these findings in the light of the clinical course of the disease, it is quite clear that the focal neurologic signs were the consequence of the infarct in the right thalamus from thrombosis of a sclerotic thalamic artery and had nothing to do with the tuberculous infection. The tuberculous meningoencephalitis present in this brain has taken a most unusual form in that the inflammatory reaction is so incomplete and unspecific, especially considering the duration of the disease. Indeed, were it

not for the presence of tubercle bacilli in the inflammatory lesions one would be hard put to identify them as tuberculous. The appearances are not those of tuberculous meningitis in the process of healing but rather of a still active infection which has been prevented from evolving in the usual way. The interesting aspect of the case pathologically is the bland non-specific tissue reaction, especially in the presence of such large numbers of tubercle bacilli. This same anomalous response was present also in the tissue about the draining sinus in the neck. The mild reaction remaining there had none of the characteristic features of tuberculous inflammation, yet in acid fast stains there were heavy masses and clusters of tubercle bacilli, and great numbers of them engulfed in macrophages.

The infection in the meninges and brain, though comparatively mild, was plainly active and could well explain the patient's increasing mental symptoms with no need to attribute them to a toxic effect of isoniazid. In fact it occasionally happens that undiagnosed mild tuberculous meningitis is uncovered at autopsy in patients dying with confusional psychosis and few, if any, signs of meningitis. Almost universal degeneration of ganglion cells in the brain might be indicative of isoniazid intoxication, but little significance can be attached to these changes especially in view of the terminal pneumonia and fever.

Dr. Ebert, would you care to make any further comments with the pathologic report in mind?

DR. EBERT: The presence of such tremendous numbers of tubercle bacilli in the neck lesion and in the meninges in the absence of a significant inflammatory response is most unusual. It would seem as though the patient had no natural immunity to tuberculous infection and no hypersensitivity. The large mononuclear cells packed with tubercle bacilli seen in sections from the cervical region suggest that the bacilli are multiplying uninhibitedly within macrophages. Recently Dr. Suter at the Rockefeller Institute has demonstrated that macrophages from immune animals can significantly inhibit the intracellular multiplication of tubercle bacilli. Certainly this patient had no immunity of this type.

Normally such large numbers of bacilli should produce tissue destruction and caseation in the hypersensitive individual. We have no information about this patient's tuberculin sensitivity, but her reaction to tuberculoprotein must have been abnormal during the final stage of her illness. Obviously she had had the ability to react to tuberculoprotein during her earlier illness, since the tuberculous infection presented itself as an abscess.

I cannot explain why chemotherapy did not control the multiplication of tubercle bacilli better than it did. We know of course that tremendous numbers of bacilli were present in the tuberculous abscess when the diagnosis was first made. I saw these smears and they looked as though they had been taken from a pure culture of tubercle bacilli. It is unusual to find such large numbers of bacilli from such lesions and often we can recover organisms only on culture. Perhaps the chemotherapy was controlling the multiplication of bacilli to some extent but in the absence of an adequate immune mechanism the effects were not so apparent. Knowing what these lesions look like pathologically I am not surprised that spread to the meninges could occur while the patient was receiving chemotherapy.

I am at a loss to explain why this patient should have this abnormal reaction to the tubercle bacillus. The suppression of the inflammatory response in the presence of large numbers of tubercle bacilli looks almost like a corti-

sone effect. Such lesions have been described in patients dying of tuberculosis secondary to massive cortisone therapy. I have seen the same type of tuberculosis after repeated courses of nitrogen mustard.

Clinically, however, there was no obvious reason for lack of resistance to tuberculous infection in this patient. She did not have any metabolic disease and I gather her bone marrow was not atrophic. I was curious about the monilia infection and asked the dermatologists if this was not an unusual case. They told me that the persistence of mouth lesions is very rare in the absence of some other debilitating illness. All we can conclude is that for reasons unknown this patient seemed to have a diminished natural resistance to infection. Dr. Richter, do you think her death resulted from an overwhelming tuberculosis?

DR. RICHTER: I would not say so. The tuberculosis in the body was neither disseminated nor massive enough to allow such a conclusion and it is scarcely possible to attribute this patient's death to the tuberculous process in the nervous system in the absence of obstruction of the spinal fluid with hydrocephalus, of cerebral edema, or other widespread cerebral circulatory disturbances. The combination of tuberculous meningitis, cerebral arteriosclerosis and terminal bronchopneumonia appears to be the most reasonable explanation of death. The possibility that isoniazid intoxication was also an important complication is certainly a good one. But I am sure that Dr. Schulman, knowing the pathologic conditions, will agree that in the face of so many complicating factors it is impossible to be sure that such toxicity existed at all or to assess its importance if it did.

The information which is furnished by the modes in which attacks commence is of great importance, practical and pathological. It is only of late that its importance has been recognized. The convulsions in idiopathic epilepsy are so rapid in their evolution, and so similar, in most cases, in their developed characters, that more observation of attacks was for a long time unproductive of much addition to our knowledge. A new error in the study of epilepsy may be said to have commenced with the investigation, by Hughlings Jackson, of the modes of onset of attacks which begin deliberately, combined with that of the subjective sensations with which attacks commence that are less deliberate in their onset — a mode of investigation which, much more than the attacks themselves, deserves the epithet "Jacksonian."

In considering this part of the subject it is important to distinguish, but not to separate, the cases in which the visible phenomena of convulsion are epileptoid, and those in which they are hysteroid. The conjoined study of the modes of onset of these two forms of convulsion is inevitable in a practical discussion of the subject.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CASE REPORT

Subarachnoid Hemorrhage and Tumor Implants from Spinal Sarcoma in an Infant

I. M. Tarlov, M.D. and Ellis B. Keener, M.D.

The case to be presented is, to our knowledge, unique in three respects. It is the first case of a spinal cord tumor causing subarachnoid hemorrhage in an infant. Second, it has the special importance of being the first case of an intraspinal tumor giving rise to an intracranial tumor, although the converse sequence is well known.[1] Third, the primary tumor was located in cervical and upper thoracic segments of the spinal cord.

André-Thomas and his co-workers[2] first reported spinal subarachnoid hemorrhage associated with a spinal cord tumor. Since then eight other such cases have been reported by Abbott,[3] by Krayenbuehl,[4] by Roger and his co-workers,[5] and by Fincher[6] (table 1). The youngest patient in this series was ten years old. The tumor site in all these cases was either at the lumbosacral or the twelfth thoracic vertebral level.

CASE REPORT

A three and a half month old white male infant was admitted to the Flower and Fifth Avenue Hospital on January 16, 1952, in extremis. The child was said to have been quite normal until one week before admission, when the parents noted a sudden onset of weakness of the upper extremities. There was also slight fever and difficult breathing. Three to four days later the child developed moderate weakness of the lower extremities and a stiff neck. The infant was cyanotic and in respiratory distress. The respiratory rate was 44, the pulse rate 140, and the temperature 104° F.

The abnormal neurologic findings were as follows: The right pupil was constricted and smaller than the left. Marked nuchal rigidity was present. There was a complete flaccid paralysis of the upper extremities and a partial flaccid paralysis of the lower extremities. The deep and superficial reflexes of the extremities and trunk were absent. Kernig's sign was present.

A lumbar puncture revealed grossly bloody spinal fluid with xanthochromic supernatant fluid. The fluid contained 1200 white blood cells per cu. mm., of which 83 per cent were polymorphonucleated cells and 17 per cent were lymphocytes. Bilateral jugular compression produced no increase in the fluid flow, which was slow.

To determine whether the source of the hemorrhage was intraspinal or intracranial,

From the neurosurgical service of the Flower and Fifth Avenue Hospital, and the department of neurosurgery of the New York Medical College, New York City.

TABLE 1
CASES OF SPINAL CORD TUMOR CAUSING SUBARACHNOID HEMORRHAGE*

Case No.	*Author and Year*	*Location*	*Age*	*Pathology*	*Outcome*
1.	*André-Thomas et al, 1930	L 2, 3	33 years	"Benign neuroglioma"	Laminectomy, followed by some improvement
2.	*Abbott, 1939	L1, 2, 3, 4	16 years	Ependymoma	Operative death
3.	*Krayenbuehl, 1947	L1, 2, 3, 4	34 years	"Neurinoma"	Laminectomy, followed by some improvement
4.	*Krayenbuehl, 1947	T-12	41 years	"Neurinoma"	Laminectomy, followed by marked improvement
5.	*Roger et al, 1949	L 4, 5	15 years	"Neuro-spongioma"	Recovery with some improvement
6.	*Roger et al, 1949	L 5, S2	10 years	"Meningioblas-toma	Laminectomy, followed by slight improvement
7.	*Fincher, 1951	T-12, L-1	37 years	Neurofibroma	Laminectomy, followed by complete recovery
8.	*Fincher	L 2, 3	12 years	Ependymoma	Laminectomy, followed by complete recovery
9.	*Fincher	L-2	18 years	Ependymoma	Laminectomy, followed by complete recovery
10.	Tarlov & Keener, 1952	C3 - T2	3½ months	Meningeal sarcoma	Diagnosis made at autopsy

*The cerebrospinal fluid was grossly bloody in all cases.

In a recent personal communication Dr. Augustus McCravey related his experience with another case of spontaneous subarachnoid hemorrhage associated with an astrocytoma of the filum terminale in a 41 year old man. McCravey's patient, like some of the others listed in the table, was in good health until, while doing some heavy lifting, he developed severe pain in his head, neck, back and lower limbs. The cause of the subarachnoid hemorrhage remained undetermined until a myelogram revealed evidence of the tumor.

the ventricle was tapped through the right anterior fontanel. The ventricular fluid was faintly blood-tinged and its supernatant fluid was clear. It was concluded that the source of the subarachnoid hemorrhage was spinal. A myelogram was done to locate the site of the hemorrhage. One and a half cc. of Pantopaque were instilled in the subarachnoid space through the third lumbar interspace. X-rays, taken with the child in the vertical head-down position, showed a complete arrest of the Pantopaque at the level of the second thoracic vertebra.

The syndrome was clearly one of spinal cord compression, the cause of which was doubtful. However, operation seemed clearly indicated. The infant was immediately taken to the operating room, but respirations ceased before the anesthesia was begun, and he died a few hours later.

Autopsy examination revealed no abnormality except that in the central nervous system. There was a firm grey mass within the spinal dura extending from the third cervical to the second thoracic segments on the right side (figure 1). The mass was covered with blood clot, which was present in the spinal subdural and subarachnoid spaces underlying the tumor. The subarachnoid blood was also present throughout the spinal subarachnoid space, and most marked in the upper thoracic and the lumbosacral areas, where it was 3 to 5 mm. thick. The external surface of the spinal dura was quite smooth; the vertebral column was entirely normal.

The tumor was firmly attached to the dura mater over the whole right half of its circumference. The spinal cord was considerably compressed by the mass. The left dorsal and ventral roots and the right dorsal nerve roots were clearly discernible within the dura, but the left ventral nerve roots could not be traced within the tumor mass, although they were visible extradurally.

On cross-section through the tumor at the site of the greatest dural bulge, which was at the sixth cervical nerve root, the tumor was approximately the same size as the spinal cord. It was adherent to the dura

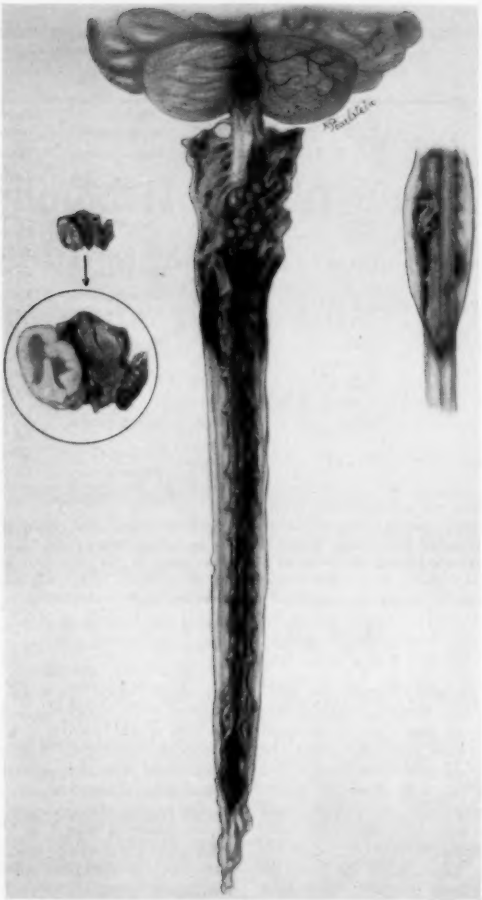

FIG. 1. Drawing of intradural spinal tumor and subarachnoid spinal hemorrhage. The ventral view of the lesion is shown on the right, and on the left a cross-sectional view through the middle of the mass.

over the entire right ventrolateral quadrant. The spinal cord did not appear to be invaded by tumor, but there was a 2 mm. layer of blood between tumor and cord at this site.

The brain showed no abnormality grossly.

The tumor consisted of a closely-packed mosaic of variegated cells. They varied from lymphocyte-like cells and fibroblasts to rather large cells with bizarre-shaped nuclei and irregular cell bodies. Considerable nuclear clumping, ill-defined giant cells and mitotic figures were visible. Varying degrees of admixture of these cell types occurred. There were moderate numbers of nuclear inclusion bodies and thin-walled blood vessels. Some of the cells forming the blood vessel walls were identical with some of

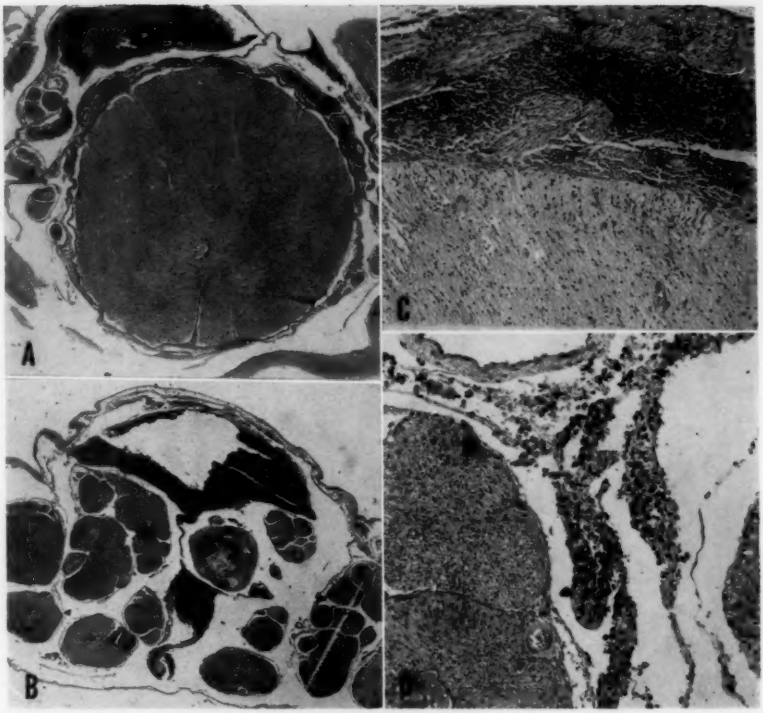

FIG. 2. Photomicrographs showing, A, the tumor attached to the dura and the subarachnoid and subdural hemorrhage; B, subarachnoid hemorrhage in the cauda equina; C, tumor cells around and in the anterior cervical nerve roots; and D, tumor cells in the subarachnoid space of the cauda equina.

the tumor cells. A few small areas of necrosis were present in the tumor. There was a delicate reticulin throughout the tumor.

The tumor appeared to arise from the inner layers of the dura mater over a broad zone (figure 2). The surface of the dura was smooth. Transitions from the elongated dural cells to the tumor cells could be easily traced.

Many of the nerve rootlets were completely infiltrated (figure 3) and destroyed by tumor cells which had invaded the pia arachnoid and in several areas were present in the spinal cord beneath the pia mater. Many of the blood vessels of the subarachnoid space and the spinal cord were engorged and rupture of thin-walled distended subarachnoid veins was discernible. There was hemorrhage in the subarachnoid space and in the white matter of the spinal cord. Hardly any polymorphonuclear or lymphocytic infiltrations had occurred around the hemorrhage or elsewhere in the tumor.

The spinal cord showed moderate vacuolization of the white matter and endothelial swelling, particularly of the subpial vessels. Weigert-Pal and Gros-Bielschowsky preparations revealed many destroyed nerve fibers in the posterolateral quadrant of the spinal cord around the spinal cord hemorrhage. The nerve fibers of some of the nerve rootlets were also destroyed. The ganglion cells of the spinal cord showed marked chromatolysis—disappearance of Nissl substances, shrinkage and peripheral migration or even loss of nuclei and of cell angularity.

Sections through the lower levels of the spinal cord and also through the cauda

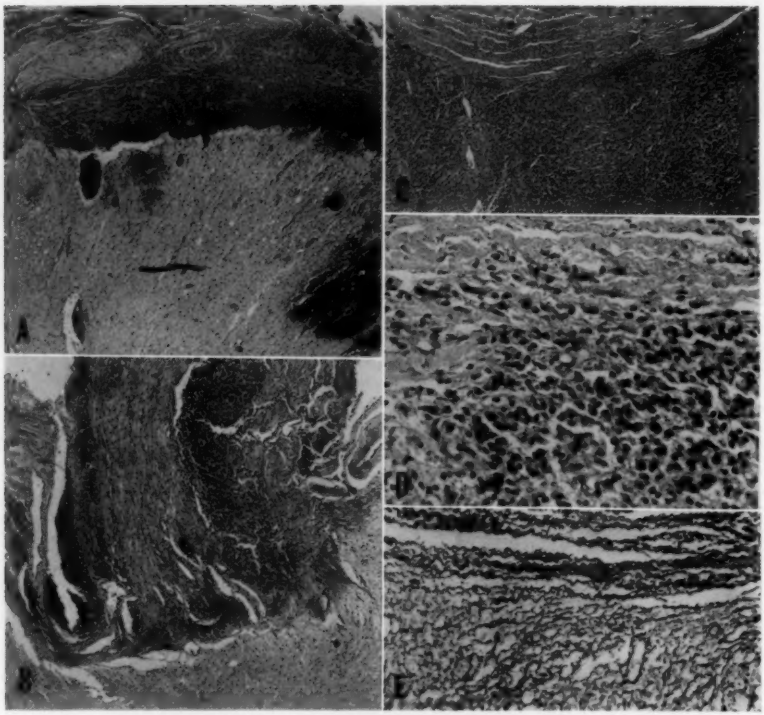

FIG. 3. Photomicrographs showing, A, subarachnoid and intraspinal hemorrhage at level of tumor; B, tumor surrounding and infiltrating posterior cervical nerve root; C, tumor attached to cervical dura mater; D, transition from dural cells to tumor cells; and E, collagen stroma of the dura and the reticular stroma of the tumor. A, B, C and D, hematoxylin and eosin stains. E, Laidlaw's lithium silver carbonate impregnation for connective tissue.

equina showed, besides hemorrhages, discrete masses of tumor cells in the subarachnoid space. Some of these neoplastic cell groups adhered to leptomeninges and nerve roots. Others were free in the subarachnoid space. These tumor implants varied from single cells to large cell sheets. Tumor cells had broken through the endoneurial sheath of nerve roots of the cauda equina and were present around nerve fibers. Tumor cells also occurred in the filum terminale externum.

Sheets of tumor cells were present in the subarachnoid space over the cerebellum, medulla, and pons, and in the cerebral peduncles. There was a nodule of tumor cells about one half cm. in diameter within the parenchyma of the under surface of the temporal lobe close to a sulcus (figure 4). Many of these cells were like lymphocytes but transitions to large irregular cells also occurred.

There were tumor cells in the subarachnoid space over the cortex as well as deep within a cerebral sulcus. Metallic impregnation preparations for astrocytes and also for oligodendrocytes failed to reveal any neuroglial cells in the tumor and Nissl preparations showed no nerve cells in it.

Comment: The tumor was clearly malignant. The transition from elongated fibroblastic cells to tumor cells showed that it was a sarcoma. A meningeal origin was indicated by the gradual transition from

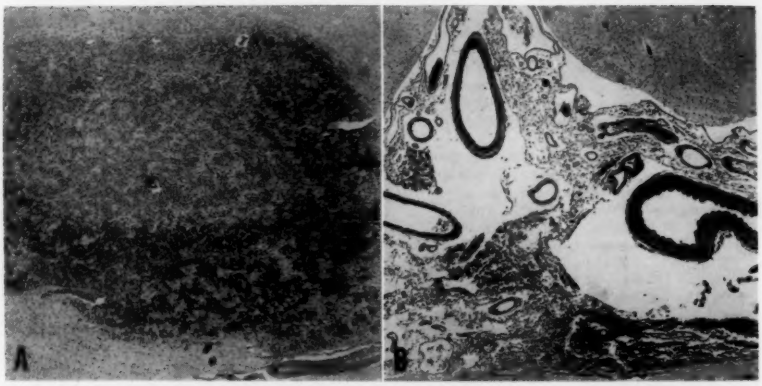

FIG. 4. Photomicrographs showing, A, tumor implant in temporal lobe and, B, tumor cells in interpeduncular subarachnoid space. Hematoxylin and eosin stains.

dural to tumor cells and the resemblance of many of the tumor cells to those forming the thin-walled blood vessels of the tumor. Our diagnosis was meningeal sarcoma with subarachnoid and spinal cord hemorrhage and spinal and intracranial-tumor implants.

DISCUSSION

Spontaneous subarachnoid hemorrhage rarely occurs in infancy, under the age of 18 months, except in the neonatal period. Barber,[7] reviewing 230 cases of spontaneous subarachnoid hemorrhage in children, reported only one case under 17 months. He did not list spinal cord tumors as a posisble cause of hemorrhage.

Spinal cord tumors in infants are also uncommon. In 1951 Mosberg[8] presented an excellent review of all previously reported cases in infants. There were 22 cases, to which he added a case with a leukemic deposit. Three of these cases were sarcomas.

The presence of single as well as groups of tumor cells in the cerebral and spinal subarachnoid space suggests that if stained smears of the cerebrospinal fluid or histologic sections prepared from the cerebrospinal fluid sediment had been examined, the diagnosis of tumor might have been made during life. Certainly, such a procedure should be carried out when subarachnoid hemorrhage or cerebrospinal pleocytosis occurs in a patient suspected of harboring an intracranial or intraspinal tumor.

SUMMARY

A case of a three and a half month old infant with gross subarachnoid hemorrhage from a cervical spinal cord tumor (meningeal sarcoma) is reported. A total of ten cases of gross, spontaneous spinal subarachnoid hemorrhage associated with spinal cord tumors have been reported to date, but this is the first such case occurring in infancy. It brings the total number of spinal cord tumors in infants up to 23. It is also unique in having been associated with intracranial tumor implants.

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Megrim then is clearly a paroxysmal and intermittent affection, but is it also a periodical one? Is there any regularity in the return of the paroxysms? If we compare different cases one with another we shall find every variety in the length of the intervals, from days to months; but there can be no doubt that in the same case a very striking regularity is often observed. Thus looking to our table of cases we see at once that with many patients the seizures return every fortnight, with others, every month, every two months, and so on; indeed for this reason headaches of this kind are frequently spoken of by patients or their friends as "periodical headaches." On the other hand we may notice many cases in which the intervals are uncertain and variable.

Tissot has expressed himself very decidedly on this point. After remarking that the complaint usually pursues a uniform course in the same individual, he continues: "With many women migraine recurs every month before and sometimes after the catamenia; with other women and many men it recurs at longer intervals, eight, nine, or ten times a year. True migraines which recur oftener than three times a month or less than four times a year are rare." "Migraine is often very regular both as to the time of its return and the duration of the attack. I have often seen it return every three months, every month, or every fortnight." He also refers to a case in which the attack returned every Monday with the greatest regularity; but it should be observed that an exact periodicity of this kind is scarcely that for which we content, and one is tempted to suspect that the diet or engagements of the preceding day may have had something to do with it. Elsewhere, speaking of other headaches, he says: "I have never seen any which had such an exact regularity, such a perfect uniformity, such a constant duration as characterize migraine."

Edward Liveling in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CASE REPORT

Carotidynia

John Campbell, M.D. and J. P. Evans, M.D.

In 1932 Temple Fay[1] introduced the term "carotidynia" to describe unilateral facial and head pain associated with aggravation of symptoms by carotid manipulation. He reported satisfactory remission of symptoms following carotid sheath resection and cervical sympathectomy. Studies by others[2–4] have varied in results. In 1947 the opinion was expressed by Olivercrona[5] that "operations upon the cervical sympathetics and the carotid sheath have fallen into disrepute."

A case with the syndrome of carotidynia with satisfactory response to resection of the trigger zone in the carotid sheath is presented here. In addition a lesion was found at operation to explain the carotid sheath irritability.

REPORT OF CASE

A 49 year old Catholic nun was seen in neurologic consultation on June 6, 1950, because of severe recurrent right hemicrania of three years' duration. Beginning in 1947 she had experienced right parietal and occipital pain beginning at 2 to 3 a.m., and continuing 12 to 14 hours. These attacks occurred one to three times a week. Partial relief was obtained with analgesics and ergot preparations. Asthma, present since 1937, complicated the headaches but was not always associated with the attacks.

In 1930 the patient had fallen on her right shoulder. A large subcutaneous hematoma involved the arm and right anterior cervical region. A year later, in 1931, an enlarged lymph node was removed from the right supraclavicular area and was followed by radium therapy. Six years later asthma made its appearance and gradually became more frequent and severe. From 1937 to 1950 large doses of adrenalin, taken to alleviate asthmatic attacks, caused bilateral frontal headaches which gave her no concern. In 1949 cyanotic episodes were noted, diagnosed as methemoglobinemia, due to the analgesics used for the relief of the hemicrania.

Psychiatric examination disclosed only mild depression. The patient felt that she should be able to work and was causing too much trouble by being ill. Manipulation of the right carotid artery below the bifurcation reproduced the right parieto-occipital pain. One per cent procaine injected into the carotid sheath inhibited this response. The attacks were immediately aborted by procaine infiltration about the trigger zone in the right carotid. There was no evidence of carotid sinus sensitivity; the left carotid artery was not involved. Clinical and laboratory study revealed no other abnormalities.

On July 17, 1950, a right carotid sheath resection was done, and the trigger zone was found by mechanical stimulation of the exposed carotid sheath. At operation fibrosis was found in the fascial planes of the neck and about the common carotid artery.

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During the subsequent two years the patient has been practically free of hemicrania. On occasions she had slight right parietal pain relieved by analgesics. At times she has had discomfort in the right parietal area when she leaned forward, and under the emotional stress of work she has noticed mild right parietal pain. The asthma has been reduced in severity. She is well adjusted in her work and has gained 11 pounds. Carotid sinus stimulation does not reproduce the pain.

This case of carotidynia is presented because of the characteristic clinical syndrome, the findings about the vessel at operation, and the satisfactory result following surgery. In spite of the present pessimism regarding cervical sympathetic and carotid sheath surgery in the treatment of migraine, it is worth emphasizing that with the proper indication, gratifying results can be obtained.

SUMMARY

A case is presented of carotid sheath sensitivity triggering recurrent hemicrania which was temporarily relieved by procaine block. Relief has been obtained for two years by carotid sheath resection.

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The fact that an aura commencing in a limb may be arrested by a ligature around the limb, above the place in which the aura is felt, was once thought to constitute evidence that the process of the convulsion originated at the periphery. It is now known that the ligature will arrest a fit which is due to a cerebral tumor as effectually and more frequently than one due to any other cause. This was first pointed out in the beginning of this century by Odier. It has been insisted on by Brown-Séquard, and I have seen many striking instances of it.

When the aura is regarded as the expression of the commencing change in the brain, its study becomes of even greater importance than when it is regarded as originating at the periphery. By this means we gain information, to be obtained in no other way, of the brain function first deranged – that is, of the functional region in which the process of the fit begins. In some cases, at least, this may be regarded as the seat of the disease. We learn also, as Hughlings Jackson has so well shown, something of the form of normal cerebral action which disease modifies, rather than subverts.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Neurology

Burton M. Shinners, M.D. 1911--1952

BURTON M. SHINNERS was born on September 28, 1911 in Dunkirk, New York. After a high school education in his native city he went to Notre Dame University, receiving a bachelor of science degree in chemical engineering in 1933. This field of activity did not satisfy him, however, so he went to Duke University where he received his M.D. degree in 1936. At Duke he became interested in neurology. Since there was no set pattern of training in the specialty at that time, he embarked upon a peripatetic course of training that included a clinical clerkship under Gordon Holmes at the National Hospital in Queen's Square, an internship at Henry Ford Hospital and an assistant residency in neurosurgery under Doctors Jason Mixter and J. C. White at the Massachusetts General Hospital. While assistant resident in medicine at Baltimore City Hospital under Doctor Frank Ford, he developed an interest in the neurologic problems of children that influenced his progress thenceforth. He served a residency in neurology at Massachusetts General Hospital under Doctor J. B. Ayer and received his psychiatric training at McLean Hospital, Waverly, Massachusetts, and at the Westchester Division of the New York Hospital under Doctor C. O. Cheney.

On this latter assignment he was first attacked by the chronic illness from which he never fully recovered. He returned to his home in Dunkirk to convalesce, and after he had recovered sufficiently came into my office as an associate. This was during the war years when the few neurologists and neurosurgeons left in private practice were deluged with work. "Mike" plunged into it with the zeal and energy that was characteristic of him, so our association in the office and in the hospital approached the ideal sought but seldom experienced by those in similar, though slightly different, fields of activity. His private practice increased to such proportions that our office became inadequate, and it became necessary for Doctor Shinners to open an office of his own.

He loved teaching and entered into the work of the department of neurology of the University of Buffalo School of Medicine, advancing to the rank of assistant professor. At the Buffalo General Hospital he became co-chairman of the division of neurology. He was made head of the division of neurology of the Children's Hospital of Buffalo in 1946,

and was an attending neurologist at Mercy and Sisters' Hospitals.

Doctor Shinners was intensely interested in electroencephalography and was an early member of the Eastern Electroencephalographic Society and later of the American Electroencephalographic Society. He developed a strong department at the Children's Hospital which he headed until his death. He did a large volume of work with the clinical electroencephalographic laboratories in several of the Buffalo hospitals. His interests in this discipline were profound and fundamental, and his pertinent literary output on the subject was limited by his predominant interest in the basic principles of the phenomenon rather than its clinical application.

His chief interests in life were his family, his work and travel. On December 27, 1937, he was married to Hildegarde Fitzgerald of Fredonia, New York. Five childern were born to them and his Irish ancestry is reflected in the names he gave them: Michael, Deirdre, Sean, Seamus and Shannon. He enjoyed returning to the land of his ancestors and on two occasions took one of his youngsters with him.

Doctor Shinners was certified by the American Board of Psychiatry and Neurology in 1944. He was a member of the American Medical Association, the Medical Societies of the State of New York, the Buffalo Neuropsychiatric Society, the American Neurological Association, the American Academy of Neurology, the American Electroencephalographic Society, the Eastern Electroencephalographic Society, Alpha Omega Alpha and Phi Chi Medical Fraternities. He took every opportunity to attend professional meetings and was as much at home among the neurosurgeons as among the neurologists, the electroencephalographers or the neurophysiologists.

In the late summer of 1952, feeling decidedly under par, he went to Ireland for a short visit and returned to New York to attend a neurosurgical meeting. He was too ill to attend and it was necessary for him to return home and to the hospital. This time the inroads of his old enemy were too great for his frail body to sustain and he died on November 11, 1952. His loss was a great one not only to his personal friends but to the field of neurology, particularly in the western New York area. His promise was great, as were his accomplishments during the all too short period we were able to enjoy them.

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Neurology BOOK REVIEWS

The Basis of Clinical Neurology

Samuel Brock, M.D. Third edition. 1953. Baltimore: The Williams and Wilkins Co. 510 pages. $7.00.

The third edition of Dr. Brock's well-known book follows essentially the same pattern as the earlier editions. It is a skillful compilation of the basic information on the anatomy and physiology of the nervous system applied to clinical neurology. In the preface the author hopefully looks forward to the day "when neurology and psychiatry will not only be quite inseparable, but will speak the same language." Nevertheless, until that day comes, he continues to speak a clear and readable neurologic language.

The anatomy of the nervous system provides the structural scaffolding upon which the experimental physiologic and clinical data are deployed. Accordingly the basic plan of the book follows in the main the traditional sequence in teaching neuroanatomy from the peripheral nerves and spinal cord, followed by the brain stem, cerebellum, thalamus and basal ganglia, to the cerebral cortex and the cerebral lobes. The discussion of special topics, such as circulation of the spinal cord, brain stem and cerebral hemispheres, the autonomic nervous system, posture and muscle tone, the cerebrospinal fluid, and topics involving a technically specialized treatment such as electroencephalography, cerebral angiography and clinical electromyography, is interpolated as sections of appropriate chapters or presented in separate chapters. The anatomical, experimental physiological and clinical information is compiled from a wide range of sources.

In the present edition more recent advances in the knowledge of the peripheral nerve degeneration, of the physiology of spinal cord and reticular formation, of disorders of perception and language disorders, and discussion of theories of consciousness, neuronal circuits and even cybernetics are included. This enormous material is diligently integrated and condensed in summaries, diagrams and synoptic tables which bespeak the author's keen sense of what is didactically relevant and effective. One may wonder at times whether this encyclopedia of neurology does not cater too much to the need of "spoon feeding," and in some sections might disappoint those who need firsthand and critical information; yet one cannot doubt the usefulness of the book as a competent and comprehensive compendium of neurology. It is a teacher's as well as a student's manual.

The validity of the book speaks for itself in the popularity of its first two editions. The third edition is substantially enlarged and revised in content and structure of several chapters with addition of several new topics which came lately into the foreground of theoretical and practical interest and attention. The preparation of special topics, such as special tests for disorders of perception,

electroencephalography, cerebral angiography and clinical electromyography was entrusted to the authoritative contributors to the book especially competent in these particular fields. Fifteen pages of bibliographic references and an index complete the book. The number of illustrations is substantially increased and their reproduction much improved through the change in the type of paper used in this edition. The book is attractively published. P.I.Y.

Neurosurgery in General Practice

Adrien Ver Brugghen, M.D. 1953. Springfield, Illinois: Charles C Thomas, Publisher. 665 pages, 282 illustrations. $14.00.

The purpose of this book, it is stated, is to help the general practitioner with his neurosurgical problems. Although written by a neurosurgeon having strong personal views, the book deliberately expresses a conservative or middle of the road viewpoint in deference to its intended readers – general practitioners – who do not have the scientific or academic background to evaluate controversial subjects in a highly specialized field. For those desiring to pursue such subjects more fully, the author gives a short list of references after each chapter.

The general plan of the book is to present in each chapter, the signs and symptoms of one subject, briefly its pathological anatomy, and then the methods of treatment. Following this review, a number of illustrative cases are presented in some detail with short pertinent comments. In this fashion, head injuries and their complications, spinal cord injuries, peripheral nerve injuries, the herniated nucleus pulposus syndrome, pain syndromes, spinal cord and brain tumors, suppurative diseases of the central nervous system, cerebral vascular diseases, the sympathetic nervous system, congenital anomalies, and miscellaneous conditions are discussed. Chapters on lumbar puncture, x-ray diagnosis and neurological examination are appended. The index is quite adequate, and the general format and composition of the book is pleasing.

The reviewer can not agree with the author who states in his preface that, "There is nothing in this manuscript that will be of interest to the neurologist or neurological surgeon; they already know what is written here." This reviewer found much in the book of great interest. In spite of the author's attempt to keep out his personal views, throughout the book in discussion of treatment and case reports, his opinions add spice to the subject matter. And on subjects still not entirely agreed upon by all neurosurgeons, his writing may profitably be read by all specialists.

However, the reviewer must confess a few misgivings that the author has fulfilled his major purpose – a book to help the general practitioner with neurosurgical problems. The reviewer had expected that the author might discuss the relationship of general practitioner to neurosurgeon answering such specific questions as: "When should I request a consultation of a neurosurgeon in a head injury case? What procedures am I, a general practitioner, justified in performing?" (There is no doubt that in cases of acute extradural hematomas, burr holes put in by a general practitioner, when a neurosurgeon is hours away, may be lifesaving, even though a secondary operation is necessary later.) Although some of these problems are mentioned briefly, they might have had more consideration. Even so, the general practitioner will find in this book the answers to many of his problems and through it, will gain

an insight into the practice of neurosurgery which should help him in the selection of cases for neurosurgical consultation and in the care of patients who have had surgery of the nervous system. The book is recommended for all neurologists, neurosurgeons and those general practitioners who wish to learn of the scope and accomplishments of modern neurologic surgery. A.E.W.

Correlative Neuroanatomy and Functional Neurology

J. J. McDonald, M.D. and J. G. Chusid. Sixth edition. 1952. Los Altos, California: Lange Medical Publishers. 261 pages, 173 illustrations, $4.00.

Of all fields of medicine, clinical neurology probably lends itself best to a correlation with the related basic subjects of neuroanatomy, neurophysiology and neuropathology. In this small volume the authors have attempted to develop clinical neurology through a discussion of these basic subjects. The choice of material is excellent and the organization of the subject matter should prove both interesting and of value to the student. The authors have done an excellent job in presenting a comprehensive view of the entire field of neurology, thus avoiding the usual artificial dissociation between the clinical and basic material. In future editions there should be some expansion of the clinical material which in this volume is surveyed a little too briefly to offer adequate coverage.

A.B.B.

Operative Neurosurgery

Elisha Stephens Gurdjian, M.D. and John E. Webster, M.D. 1952. Baltimore: The Williams and Wilkins Company. 442 pages. $10.00.

The spectacular development of neurosurgery in the first half of the twentieth century has been so rapid that textbooks in this field could not be written before they were out-dated. This book is the first attempt to present a text of operative surgery in this field. It is well planned and executed and presents the basic anatomic, diagnostic and technical information for the common operative procedures of neurologic surgery. Extensive anatomic descriptions add to the reference value of the work. The techniques described are those used by the authors. The procedures advised are in most cases those used by the majority of neurosurgeons, although a few exceptions can be made. Relief of intractable pain in the upper extremity is not best treated by posterior rhizotomy as the authors suggest. This procedure leaves the patient with a useless, flail limb. Medullary tractotomy or high cervical cordotomy gives satisfactory relief of pain with much less disability and in competent hands, the superior results of these procedures justify their increased risk.

The work is divided into anatomic headings: head, spine, autonomic nervous system, and peripheral nerves. The surgical treatment of trauma is properly emphasized. It is not clear how often the authors carry out operative procedures on patients with skull or brain injuries as the only figure they quote includes the treatment of uncomplicated scalp lacerations. Some subjects are not given adequate treatment. Both psycho-

surgery and intracranial aneurysms deserve more consideration and a more critical and detailed presentation.

An outstanding feature of the work are the diagrammatic, multiple action, multiple plane drawings of Miss P. La Riviere. These unusual illustrations gave the reviewer much pleasure. They will make the text much more vivid and intelligible to the experienced surgeon or trained anatomist, but it is feared that the more complicated ones may confuse the student or the young surgeon. The artist's enthusiasm for the possibilities of her technique has on occasion led to illustrations which are so distorted and complicated as to confuse anyone who is not already familiar with the structure depicted.

This is a well planned and organized work which has been meticulously executed. No typographical errors were found and only rare discrepancies or inaccuracies were noted. It is highly recommended to all neurosurgeons. Every neurosurgical resident and young neurosurgeon should study it thoroughly.

H.C.V.

Diseases of the Nervous System

F. M. R. Walshe, M.D., D.Sc., F.R.S. Seventh edition. 1952. Baltimore: The Williams and Wilkins Company, 365 pages. $5.50.

A reading of the recent edition of this well-seasoned work gives the teacher of neurology a convenient opportunity of surveying his program in terms of the clearly defined goal set down by the author — a "practical guide to students and practitioners" which proposes "to deal only with what is possible to general practitioners in the matter of diagnostic methods and treatment." It appears to the reviewer that the author has used good judgment in the selection of subject matter and has adhered carefully to his objective. Testing the practical aim of the book, a check of recent State Board and National Board questions indicates that the text is adequate for these.

There are no references to the literature. A sampling of student opinion indicates that in the preparation for clinical pathologic conferences the book is not always equal to many questions raised nor does it indicate where the information may be found. Those students, however, who in their practice remember the general content of this work would without doubt do extremely well by their neurologic patients.

In the classical tradition of clinical neurology textbooks, there is a concluding chapter on psychoneurosis. Here, the incisive writing of the author comes to the fore. It may be recalled that in his Linacre lecture of 1950 the author considered the place of psychological medicine in the scheme of learning and found that it was properly a mode of history rather than a mode of natural science; here he finds that the need for a discussion of psychoneurosis in a textbook of clinical neurology is not for the purpose of explaining origins or of indicating psychologic therapy but for the imperative requirement of making a correct diagnosis.

A.R.V.

Neurology

Familial Primary Amyloidosis with Nervous System Involvement

Artin D. Kantarjian, M.B., Ch.B.
and Russell N. DeJong, M.D.

PRIMARY AMYLOIDOSIS is a rare systemic disease; a total of about 80 cases have been reported in the literature.[1] In the majority of cases the predominant involvement has been in the heart, lungs, striated musculature, gastrointestinal tract, tongue, and blood vessels, or in tissues primarily of mesodermal origin, and death is usually the result of cardiac changes. It is most commonly a disease of the older age group, and the average age at which the symptoms reach clinical importance varies from 52[16] to 55.[18] The etiology is not known, and an inherited tendency is rare; the first report of familial amyloidosis is that of Ostertag in 1950.[2]

The presence of nervous system involvement in amyloidosis has been recognized on only a few occasions. Königstein and Spiegel and Königstein,[3] in 1924, reported the case of a 60 year old man in whom dysphagia and atrophy, and paralysis of the muscles of the arms and hands appeared after an attack of erysipelas; amyloid was found in the epineurium and vessels of the peripheral nerves, as well as in the muscles. The authors expressed the belief that the latter involvement accounted for the symptoms. The first detailed account of extensive nerve involvement in amyloidosis is that of De Navasquez and Treble,[4] who in 1938 described the case of a 36 year old man with peripheral

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Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 11, 1953.

neuropathy, diarrhea, urinary retention and cardiac failure. Neurologic findings included pupils which did not react to light, profound atrophy and paralysis of the extremities, and areflexia in the lower limbs. Cerebrospinal fluid examination showed a protein of 160 mg. and a colloidal gold curve of 2443333200, but no increase in cells. Pathologically there were widespread amyloid deposits in the heart muscle, submucosa of the intestinal tract, and blood vessels, as well as in the nerve roots, peripheral nerves, and sympathetic ganglia; the brain and spinal cord were not affected. Götze and Krucke,[5] in 1941, described the case of a 64 year old man with muscular weakness and atrophy, paralysis, paresthesias, incontinence and impotence. The protein content of the spinal fluid was 22 mg. There were amyloid deposits in the peripheral nerves and ganglia as well as in the vessel walls of the cerebellum, brain stem and brain, with focal "granular" atrophy of these structures.

Kernohan and Woltman,[6] in 1942, described the case of a 50 year old man with weakness of the extremities, left facial palsy, pain and diarrhea, who was diagnosed as having peripheral neuritis. He died suddenly, and at autopsy was found to have widespread amyloid deposits in the blood vessels, in many places spreading beyond the media and through the adventitia into the surrounding tissues, with parenchymatous changes in various organs secondary to ischemia. The results of these infiltrations were best seen in the peripheral nerves, where there was an extensive ischemic degeneration. Findley and Adams,[7] in 1948, reported the case of a 46 year old man with anorexia, constipation, insomnia, impotence, loss of weight and marked hypersensitivity of the skin. He exhibited the sensory and reflex changes of a peripheral neuritis; spinal fluid examination showed a protein of 43 mg. and a colloidal gold curve of 1111120000. There was heavy infiltration of amyloid in the nerve trunks, peripheral nerves, perineural tissue, and sympathetic ganglia. Jones and Frazier,[1h] in 1950, summarizing 15 cases of primary cardiovascular amyloidosis all over the age of 55, mention neurologic symptoms and signs in a large percentage. Two had numbness of the fingers and hands, one had numbness and tingling of the legs, one had weakness of the legs, and one had progressive loss of muscle function terminating in dysphagia. In only two, however, were amyloid infiltrations found in the peripheral nerves. Six of the 15 died of cerebrovascular accidents, but there were no amyloid deposits in the cerebral vessels.

Fisher and Preuss,[8] in 1951, described the case of a 62 year old man with cardiac symptoms and progressive polyneuritis; there were deposits of amyloid in the peripheral nerves, nerve roots, and sympathetic ganglia. Denny-Brown,[9] in 1951, described in detail a family, originally reported by Hicks,[10] with hereditary sensory radicular neuropathy. He found in one member of this family, on whom exhaustive pathologic studies were carried out, hyaline masses around the capillaries in certain of the dorsal root ganglia which gave a weak staining reaction for amyloid. No amyloid deposits were found in any of the body organs. He expressed the belief that the amyloid changes were

secondary to some unknown metabolic defect, and that the degeneration of the nerves in this case was similar to but distinct from amyloid neuritis. In this same article, however, the author does mention that he has observed two cases of amyloid neuritis, similar to those described by De Navasquez and Treble, and Kernohan and Woltman, and includes a section from a dorsal root ganglion of one of them to show the similarity to the findings in his case of hereditary neuropathy.

A critical review of all of the cases of primary amyloidosis that have been reported in the literature reveals that isolated instances of focal involvement of the brain and infiltration of individual peripheral nerves and sympathetic ganglia have been described. Most authors have emphasized, however, that when amyloid is found it lies in vessels or supporting tissue and does not cause primary degeneration of nerve fibers.[6] Izquierdo, Cowen and Wolf,[11] in a recent discussion of the subject, state that about 17 cases of amyloid deposition in the peripheral nerves associated with generalized amyloidosis have been recorded. They describe the case of a 52 year old man with pain, fasciculations and atrophy in the extremities, in whom there was amyloidosis with nerve degeneration as well as deposits in the blood vessel walls and mesodermal nerve sheaths of the autonomic ganglia and nerves. They state further that it is possible that such involvement is more common than the data would indicate, as often such changes are not specifically sought for in pathologic material.

Of special interest in consideration of the present cases is a recent report by Andrade[12] of a number of cases of generalized atypical amyloidosis with predominant involvement of the peripheral nerves. This condition was found to be prevalent in certain districts of Portugal, and the familial nature of the disease was observed. The cases reported had the following clinical characteristics: 1.) Insidious onset with progressive lowering of the general state of health. All those reported in detail were young adults. 2.) A severe peripheral neuropathy, predominantly of the lower extremities, with sensory impairment, muscular atrophy and paralyses, areflexia, trophic ulcerations, and disturbances of the sphincters. Associated nervous system alterations included anisocoria with poorly reacting pupils. Premature impotence was a common finding. Hyperalbuminosis of the cerebrospinal fluid was found in six cases. 3.) Gastrointestinal symptoms, including both constipation and diarrhea. 4.) Generalized amyloidosis, with most pronounced involvement of the peripheral nerves and the kidneys. In the former there was a severe degeneration of the myelin sheaths, with secondary destruction of the axis cylinders and proliferation of the Schwann cells.The degeneration was accompanied by deposits of amyloid within the nerve bundles. The spinal cord showed only slight degeneration of the posterior columns and retrograde changes in the anterior horn cells.

We have recently had the opportunity of studying the cases of two sisters with a clinical syndrome which included a severe peripheral neuropathy,

spinal fluid alterations, ocular changes, and gastrointestinal and endocrine symptoms. Autopsy studies on one showed evidence of generalized amyloidosis. Incomplete clinical and postmortem reports on the father revealed that he had died of a similar syndrome.

REPORT OF CASES

Case 1. A 25-year-old married woman was first a patient in the University Hospital from April 20 through May 9, 1948, and was hospitalized on two further occasions—from August 8 through November 19, 1949, and from February 5 through April 9, 1951. At the time of her first admission she complained of difficulty in walking, especially at night, of one year's duration, anorexia and vomiting spells of nine months' duration, blurring of vision for three months, and loss of control of urine for about one month. It was stated that she had had exophthalmos for five or six years, and about 14 months before admission she was hospitalized for what were described as symptoms typical of hyperthyroidism, and a thyroidectomy was performed. She made an uneventful immediate postoperative recovery, but a few months later began to have difficulty in walking, and shortly thereafter developed anorexia and vomiting. She had lost 40 pounds in weight.

At the time of her first admission the patient was noted to be a poorly nourished woman who appeared to be older than her stated age. Her temperature was 98, pulse 84 per minute, respirations 20 per minute, and blood pressure 114/84. She was 5 feet 4 inches tall and weighed 100 pounds. There was bilateral exophthalmos, with extensive vitreous opacities; patches of exudate were seen along the retinal vessels. The pupils were dilated and unequal; they reacted in accommodation but not to light. There was minimal constriction of the visual fields. The isthmus of the thyroid was enlarged and firm. The heart was moderately enlarged and there was a harsh presystolic and systolic murmur heard to the left of the sternum. The liver was enlarged 1 cm. below the costal margin and there was tenderness in the abdomen on deep palpation. There was peripheral blunting of pain and temperature sensations in the lower extremities, and position and vibration sensations were lost at the feet and ankles. There was generalized muscular hypotonia with diffuse weakness, but without atrophy or fasciculations. The Romberg test was positive. The gait was of the steppage type. The biceps reflexes were weakly present. The triceps, patellar and achilles reflexes were absent.

Laboratory examinations showed a hemoglobin of 12 gm. with 3,970,000 red blood cells per cu. mm. The urinalysis was normal, including tests for porphyrin bodies. The blood Kahn test was negative. The basal metabolic rate was minus 9 per cent. The spinal fluid contained 4 cells per cu. mm., with a negative Kahn reaction, a total protein of 200 mg. per 100 cc., and a colloidal gold curve of 0112211000. X-rays of the chest, skull and gastrointestinal tract were normal, as well as retrograde pyelograms. Gastric analysis was normal, as was the tuberculin test. The diagnosis at this time was peripheral neuritis secondary to anorexia nervosa and vitamin deficiency. The ocular findings were not adequately explained. The patient seemed to improve on vitamin therapy and she was discharged on this regimen.

At the time of the second admission it was stated that all of the symptoms and signs noted before had progressed. The vomiting had continued, the difficulty in walking was more marked, and the vision was increasingly impaired; there had been amenorrhea for 15 months, and there had been increasing loss of weight. At this time the patient weighed 93 pounds. Atrophy and weakness of the extremities was much more marked, so that walking was extremely difficult, and the exophthalmos was more pronounced. A very loud blowing systolic murmur was heard over the entire precordium, and an electrocardiogram showed evidence of myocardial damage. The patient, in addition, had large sacral decubiti with secondary infection, as well as excoriations over the feet and legs. Therapy, on this occasion, was similar to that which had been carried out previously, although treatment

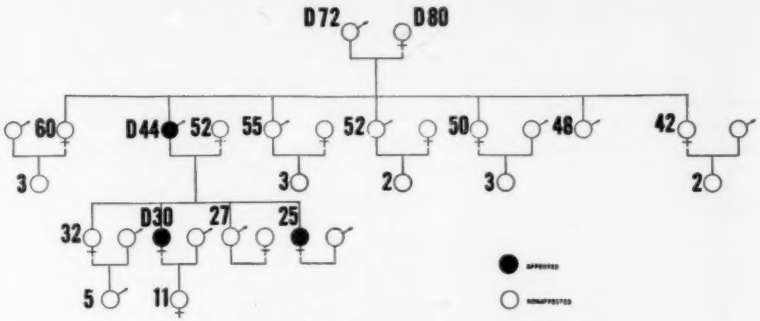


FIG. 1. Geneologic chart showing four generations of family.

was complicated by the necessity of caring for and repairing the decubiti.

At the time of the third admission there was still further increase in the symptomatology, and, in addition, the patient was markedly agitated and depressed. Most of this hospitalization was spent on the psychiatric service. She weighed 80 pounds. She had extensive atrophy and paralysis of the distal portions of both upper and lower extremities, with resulting flexion contractures and trophic changes in the skin. She had marked proptosis bilaterally, with exposure keratitis and absent vision. At times she was incontinent of both urine and feces.

Laboratory tests carried out during this third hospitalization were as follows: An electroencephalogram showed a moderately severe diffuse abnormality with no evidence of a specific localized lesion. The basal metabolic rate was minus 16 per cent, with a total serum cholesterol of 182 mg. per cent. The total serum protein was 7.0 per cent, with albumin 4.4 per cent, globulin 2.6 per cent, and an albumin-globulin ratio of 1.7. Spinal fluid examination showed a total protein of 180 mg. per 100 cc., with a colloidal gold curve of 0001111100. Biopsy of the skin and muscle showed atrophy of voluntary muscle with fatty atrophy of the muscle fibers. There were basophilic changes in collagen of the dermis of the skin, but there was no evidence of disseminated vascular disease. The connective tissue was reported to show mucinous change with metachromasia in methyl violet stain, but the findings were not considered to be typical of amyloidosis. A tarsorrhaphy was performed on the right because of corneal ulceration. The patient was discharged unimproved.

A family history taken at this time revealed that the patient's father had died of pneumonia at the age of 44 following an illness characterized by difficulty in walking, vomiting, and constipation. The mother was living and well at the age of 50, and one brother aged 25 and one sister aged 30 were both living and well. However, a sister of the patient, at that time 23 years of age, was having symptoms similar to those which the patient noted at the onset of her illness. No other members of the family were known to have had a similar illness (figure 1).

The patient died in her local hospital on October 13, 1952, about 18 months following her last discharge from the University Hospital. An autopsy was carried out there, but the material was sent to the University Hospital for examination. The following significant changes were found: The heart showed marked mucoid degeneration of the interstitial tissue with amyloid deposition about the vessels of the myocardium (figure 2). Many of the blood vessels throughout the lungs contained amyloid in their walls. There was an extremely heavy deposition of amyloid between the acini of the thyroid gland (figure 3)

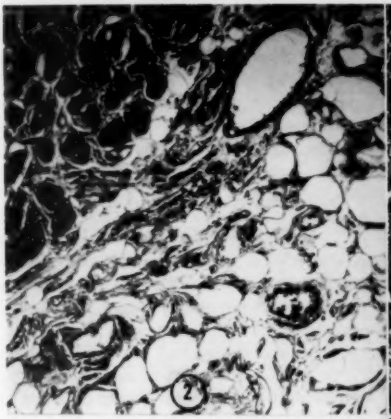
and an extensive deposition of amyloid in the spleen (figure 4). There was amyloid deposition in the mucosa, submucosa, and in the nerve plexus between the muscular coats of the small intestine (figure 5), and in the same areas of the stomach. There was heavy amyloid deposition in the pancreas, with scant deposition in the liver. There was advanced amyloidosis of the adrenals and of both the medulla and cortex of the kidneys. There was amyloid deposition about the vessels of the uterus and ovaries. No individual peripheral nerves were removed for examination, but inspection of the nerves within the various viscera, especially the heart and kidneys, showed amyloid infiltration within the perineurium and epineurium (figure 6). The pathologic diagnosis was primary amyloidosis, with especially heavy deposition of amyloid in the kidneys, pancreas, thyroid and spleen.

Case 2.—A 23 year old unmarried woman, a sister of case 1, was studied at the University Hospital on two occasions—from October 3 through October 22, 1951, and from August 10 through August 30, 1952. During the year prior to her first admission she had noticed progressive blurring of vision in the right eye, weakness of the legs with frequent falling, and severe chronic constipation. In May 1951 she had been hospitalized elsewhere for ten days with symptoms of fever and chills. She was treated with penicillin and sulfonamides, but the latter had to be discontinued because they caused vomiting. Following this illness she had recurrent periods of anorexia and vomiting, as well as oligomenorrhea, with her periods lasting only one day. She had lost 15 pounds in a period of five months.

Examination at the time of her first admission showed the patient to be a chronically ill, undernourished woman with lack of subcutaneous fat in both the upper and lower extremities. She was tense, apprehensive, and depressed in mood. Her height was 5 feet 7 inches, and she weighed 112 pounds. The temperature was normal, pulse 88 per minute, respirations 24 per minute, and blood pressure 128/90. There was bilateral exophthalmos. The pupils were dilated, somewhat unequal, and reacted in accommodation, but neither directly nor consenually to light. The ocular movements were normal. There were bilateral vitreous opacities and white retinal exudates, more marked on the right. The visual acuity was diminished on the right, on which side the visual field was constricted and there was a central scotoma. There was diffuse nodular enlargement of the thyroid gland. The heart was moderately enlarged to the left and there was a harsh systolic murmur heard just to the left of the sternum. No abdominal masses were palpated. The patient walked with an unsteady, steppage gait. The deep reflexes were normal in the upper extremities, but the patellar and achilles reflexes were absent. No sensory changes were reported.

The abnormal laboratory findings were as follows: The hemoglobin was 10.6 grams, with a red blood cell count of 4,100,000 per cu. mm. Examination of the cerebrospinal fluid on October 10, 1951, showed 21 lymphocytes per cu. mm., a total protein of 230 mg. per 100 cc., and a colloidal gold curve of 0012334100. Cerebrospinal fluid examination on October 15, 1951, showed 10 lymphocytes per cu. mm., a total protein of 170 mg. per 100 cc., a colloidal gold curve of 0001221000, and a negative Kahn reaction. The basal metabolic rate was minus 17 per cent, with a total serum cholesterol of 155 mg. per cent. The 17-ketosteroids were 3.5 mg. in 24 hours and the estrogen excretion was less than four rat units in 24 hours. No electrocardiogram was done, but a medical consultant expressed the belief that the murmur represented either an interventricular or interauricular septal defect, probably on a congenital basis. An electroencephalogram was reported as showing a generalized fast, low voltage pattern with no specific localization. Normal laboratory examinations included x-rays of the skull, chest, and gastrointestinal tract; glucose tolerance test; urinalysis, including Watson test for porphyrin bodies; blood Kahn test; a biopsy of the skin and voluntary muscles; tuberculin test and examination of both the sputum and the gastric contents for tubercle bacilli; gastric analysis, and multiple blood chemistry examinations, including non-protein nitrogen, serum amylase, serum calcium, inorganic phosphorus, plasma chlorides, and serum sodium.

During the patient's first hospitalization she had frequent periods of depression with



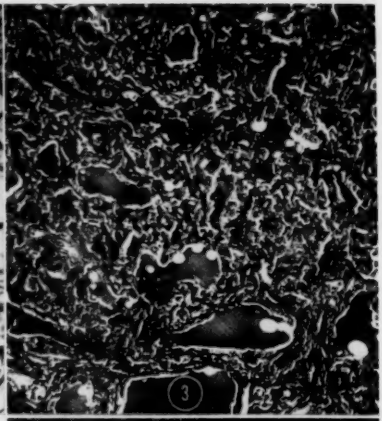


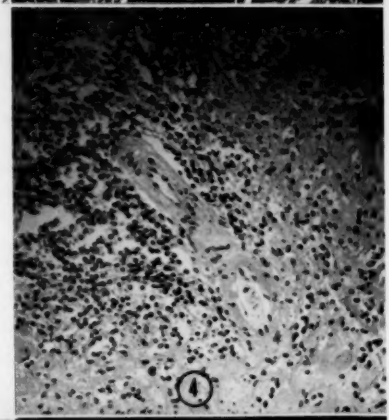
FIG. 2. Heart showing myocardial fibers, subepicardial fat and blood vessels ringed with a deposition of amyloid. Methyl violet stain.

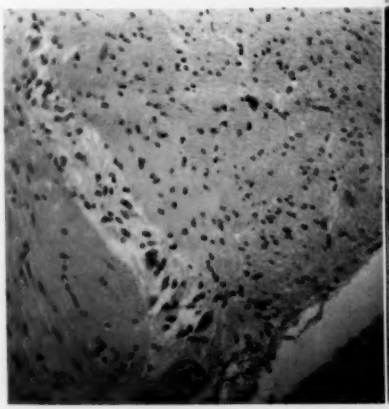
FIG. 3. Thyroid gland showing heavy deposition of amyloid between the acini. Methyl violet stain.

FIG. 4. Spleen showing extensive deposition of amyloid in the walls of the sinusoids. Hematoxylin and eosin stain.

FIG. 5. Duodenum showing amyloid deposition in nerve plexus between the layers of the muscularis propria. Hematoxylin and eosin stain.

FIG. 6. Nerve from kidney showing amyloid deposit infiltrating the perineurium and superficially the epineurium. Hematoxylin and eosin stain.





crying and anorexia, but there was very little vomiting. She was given moderate sedation and because of the lowered metabolic rate, in spite of thyroid enlargement, she was given 65 mg. of desiccated thyroid extract daily. She was also given large amounts of mixed vitamins, especially Vitamin B complex, both parentally as well as by mouth, and liver and iron. She was placed on a high caloric diet. Her general condition improved somewhat and she showed general gain in strength. She was discharged with the medications she had been receiving during hospitalization.

At the time of the second hospital admission, ten months later, the patient reported that she had recently been married, but there had been progressive visual loss, increase in anorexia and vomiting with more marked loss of weight, progressive weakness of the legs to the stage where the patient walked with marked difficulty, and recurrent epigastric pain with severe constipation. There had been no menstrual periods since her previous hospitalization. Examination at this time showed the patient to be profoundly emaciated as well as depressed. She weighed 99 pounds. The exophthalmos was more pronounced; vision was markedly decreased, especially on the right; the vitreous opacities had increased, making visualization of the retina very difficult bilaterally. In general, the physical examination was similar to that at the time of the previous admission, the outstanding change being a marked increase in her neurologic status. Her speech was slow and she spoke almost in a whisper. There was generalized atrophy, hypotonia, and weakness of the skeletal muscles, especially of the extremities, but no fasciculations. There was impairment of light touch, superficial pain, and temperature sensations in the fingers and peripheral blunting of these sensations in the feet and legs extending up to the mid-calf region. Proprioceptive sensations were absent below the knees. The Romberg test was positive. There was a complete loss of dorsiflexion of the feet. There were superficial ulcerations on the legs and feet. The deep reflexes were diminished in the upper extremities and lost in the lower extremities. The basal metabolic rate was minus 5 per cent. Spinal puncture showed the cerebrospinal fluid to contain 3 cells per cu. mm., the total protein was 160 mg. per 100 cc., and the colloidal gold curve was 0012211000.

The patient again showed slight improvement with sedation and vitamin therapy. Thyroidectomy was considered, but in view of the poor results of thyroidectomy in her sister, this was not carried out. The patient was discharged on essentially the same regimen as she had been given following her previous admission.

Case 3.—The father of the above two patients died in the Veterans Administration Hospital at Wood, Wisconsin on May 8, 1938. He had first been admitted there on June 1, 1934, complaining of pains in the legs and feet and severe constipation of about two years' duration, with loss of 25 pounds in weight during that period of time. The admission examination had shown the patient to be a cachectic man, weighing 125 pounds. He had bilateral exophthalmos and his pupils did not react to light; there was stocking anesthesia of both legs, with beginning atrophy of the interosseus muscles of both hands and of the calf muscles, loss of vibratory sense at the ankles, a positive Romberg test, and absent achilles reflexes. The spinal fluid examination showed a 1 plus Wassermann, 6 cells per cu. mm., and a colloidal gold curve of 1233333210.

During the following four years the patient was admitted to the above hospital on four separate occasions and when last admitted on March 17, 1938, he complained of progressive weakness of his legs, severe nausea and vomiting, and inability to urinate or move his bowels. His hemoglobin at that time was 75 per cent, with a red blood cell count of 3,700,000 per cu. mm. The basal metabolic rate was minus 8 per cent. There was achlorhydria. The blood Wassermann was negative. It was felt that the patient had cerebrospinal syphilis with a tabetic syndrome, although pernicious anemia with combined sclerosis was also considered.

At autopsy the patient was found to have amyloid changes in the spleen and kidneys, diffuse atrophy of voluntary musculature, pigmentation of the adrenal cortex, and cloudy

swelling of the heart and liver. In addition there was chronic glomerular nephritis and hypostatic pneumonia. Examination of the spinal cord showed fibrosis of the anterior segments and posterior horns. The peripheral nerves were not studied.

DISCUSSION

All three of the patients described above showed, to a greater or lesser degree, a similar syndrome characterized by the following clinical manifestations: 1.) Insidious onset of symptoms of a relentlessly progressive, widespread disease after the second decade. 2.) Neurologic symptoms and signs compatible with a severe, progressive peripheral neuropathy. There was not only involvement of the motor nerves to the skeletal musculature and the sensory nerves, but also of the autonomic nervous system, resulting in sphincteric disturbances and trophic lesions. Accompanying this peripheral neuritis were spinal fluid changes characterized by a marked elevation in the total protein and nonspecific changes in the colloidal gold curve. 3.) Gastrointestinal symptoms characterized by anorexia, severe nausea, vomiting, constipation, abdominal pain, and loss of weight. 4.) Ocular changes consisting of loss of vision, vitreous opacities, retinal exudates, progressive exophthalmos, and pupils which did not react to light. 5.) Endocrine changes manifested by enlargement of the thyroid with exophthalmos but a low basal metabolic rate, together with amenorrhea and changes in the estrogen and 17-ketosteroid excretion in the women, and probably impotence in the man. 6.) A systolic murmur similar to that found in congenital heart disease. Postmortem examinations have been carried out on two of the three patients, but unfortunately neither of the autopsies was complete and in neither was there adequate examination of the peripheral nerves. In both cases, however, there was evidence of diffuse primary amyloidosis.

Amyloidosis has been classified into four groups, as follows:[1h] (1) primary amyloidosis, (2) secondary amyloidosis, usually associated with chronic suppuration or tuberculosis, (3) amyloidosis associated with multiple myeloma, and (4) tumor-forming amyloidosis. The primary type is also spoken of as idiopathetic, indicating its unknown etiology, and as atypical or para-amyloid, because of its variable and atypical staining reactions. As stated above, primary amyloidosis affects mainly muscular and mesodermal tissues, occurs mainly in elderly people, and except for Ostertag's[2] and Andrade's[12] cases, is not familial. The patients reported herein undoubtedly had primary amyloidosis, but are examples of an extremely interesting and rare syndrome. The clinical course was almost identical in all three. They resemble most closely the cases described by De Navasquez and Treble[4] and Andrade.[12] Noteworthy characteristics were the age at onset and the involvement of ectodermal tissues. The genetic nature of the disorder in this family cannot be disputed, and though specific information is known regarding only two generations, the disease may be assumed to be inherited as a simple Mendelian dominant. Unfortunately detailed genetic observations were not made in Andrade's cases, although he states that he has studied 12 families with the disorder, and

in two families he was able to examine patients of two generations. The cases of hereditary sensory radicular neuropathy reported by Denny-Brown[9] were also inherited as a simple Mendelian dominant, but failed to show the evidences of generalized amyloidosis apparent in these cases, and also lacked the ocular, endocrine, and other characteristic symptoms.

It is entirely possible, as stated by Izquierdo, Cowen and Wolf,[11] that more detailed pathologic studies may show that nervous system involvement in amyloidosis is more common than has hitherto been suspected. De Navasquez and Treble,[4] for instance, in discussing their own case, mention one of DeBruyn annd Stern[13] that had been diagnosed as progressive hypertrophic neuritis. On reviewing the pathologic material on this case, which could no longer be stained for amyloid, they noted nodular deposits in the peripheral nerves and infiltrations in the walls of the arteries and within the perineurium of nerves which they felt were typical for amyloid.

SUMMARY

A family is reported in which three members showed a similar syndrome consisting of a severe peripheral neuropathy and sphincteric disturbances and trophic lesions, cerebrospinal fluid alterations, gastrointestinal symptoms, exophthalmos with vitreous opacities, endocrine changes, and cardiac abnormalities. Autopsies on two members of the family showed generalized primary amyloidosis.

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One form of remedial agency which may be conveniently noticed in connexion with the hygienic treatment of megrim, and which occasionally proves of signal service in some varieties of the complaint, as it does also in asthma, neuralgia, and other neurosal affections, is a thorough change of locality or climate. No doubt the good effect is due in some cases to removal from a malarious or otherwise unhealthy locality; and as we have seen that both megrim and asthma are remarkable for their response to particular atmospheric states, which often prove the exciting causes of the seizures, we can readily suppose that a change of residence or of climate may remove the sufferers from some equally subtle and inappreciable influence, which has been sufficient, nevertheless, to determine the attacks. In other cases the benefit must be referred to a concomitant change of habits, or to the favourable influence of change on the general nutrition.

Tissot says that he was acquainted with a clergyman who had suffered ever since he was very young from attacks of severe megrim, which was also hereditary. He went to be vicar for seven years in a mountainous part of the country, and while there was completely free from his malady, which returned again on his leaving the district. The same writer mentions that long voyages have sometimes been of service, and I may add that one of my patients, R. W., found his attacks immediately lessened and ultimately cured by going to sea for some years, and another was benefited for a time by a short voyage. It is worth noting under this head that the author of the interesting "Journal of an Asthmatic," to which I have so frequently referred, was finally cured of his asthma by a voyage to Tasmania and a residence of some years there.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Quantitative Determination of Gamma Globulin in Cerebrospinal Fluid

Its Application in Multiple Sclerosis

Elizabeth Roboz, Ph.D., Walter C. Hess, Ph.D
and Francis M. Forster, M.D.

THE cerebrospinal fluid of patients with multiple sclerosis is reported to have an abnormal protein pattern. When the proteins were separated by electrophoresis it was found that the gamma globulin fraction was responsible for the positive colloidal gold reaction.[1] This reaction and other chemical tests applied to the diagnosis of multiple sclerosis have the disadvantage of being only of a qualitative nature. This paper describes a quantitative micromethod for the determination of gamma globulin in spinal fluid, and the results of its application to spinal fluids of patients with multiple sclerosis. The method is based upon a reaction between gamma globulin and zinc sulfate in a barbital buffer reported by Kunkel.[2] The procedure has been applied to cerebrospinal fluid by Donovan et al.[3] who estimated the gamma globulin as one, two, three or four plus.

EXPERIMENTAL DATA

Evaluation of the procedure of Donovan et al.[3] Aliquots of a solution of pure gamma globulin of known concentration were precipitated with zinc sulfate dissolved in barbital buffer at pH 6.9 as recommended by Donovan. The suspension was centrifuged after standing at room temperature for four hours. The precipitate was redissolved in sodium carbonate solution and the gamma globulin determined by the colorimetric method of Folin and Ciocalteau.[4] It was found that only 45 per cent of the gamma globulin was precipitated. Therefore, it became necessary to study all the factors involved in the reaction between gamma globulin and zinc sulfate in order to determine the conditions required for quantitative precipitation of the protein.

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Presented at the fifth annual meeting of the American Academy of Neurology, Chicago, April 10, 1953.
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Reagents:

Solutions for the precipitation of gamma globulin.

1. Zinc sulfate in barbital buffer pH 7.3, containing 1.45 gm. zinc sulfate, 3.60 gm. barbital, 1.50 gm. sodium barbital in one liter of distilled water.
2. Reagent 1 diluted with an equal volume of water.
3. A 1.2 per cent aqueous sodium carbonate.

Solutions for the colorimetric reaction.

1. 0.05 per cent aqueous copper sulfate.
2. 12.5 per cent aqueous sodium carbonate.
3. Phenol reagent as prepared by Folin-Ciocalteau.[4]
4. 95 per cent ethyl alcohol.

Procedure. Pipette 2 to 5 ml. of cerebrospinal fluid into a 15 ml. graduated pyrex centrifuge tube, add an equal volume of cold zinc reagent 1 and 0.2 ml. of ethyl alcohol. The mixture is stirred well and after standing about ten minutes it is stirred again. The glass rod is washed with a few drops of the reagent and removed. The top of the tube is covered with parafilm and stored for 12 hours in a refrigerator. The centrifuge tubes are then placed in cold cups and centrifuged for ten minutes. The precipitate is washed with cold zinc reagent 2, the volume is adjusted to the original volume of the spinal fluid employed with additional reagent and centrifuged for five minutes. It was found that two such washings with zinc reagent 2 were sufficient to remove the protein of the supernatant fluid.

The precipitated gamma globulin, which is present in only minute quantities, is tightly packed and has to be dissolved with great care, using 1 to 2 ml. of the 1.2 per cent sodium carbonate solution, tapping the precipitate with a pointed glass rod. After the globulin is dissolved the glass rod is washed with the sodium carbonate solution and removed. The tube is then filled to the 5 ml. mark with the same carbonate solution and the globulin is determined colorimetrically by a modification of the Folin-Ciocalteau method.[4]

A 2 ml. aliquot of the solution is pipetted into a large pyrex test tube, and 2 ml. of the 0.05 per cent copper sulfate solution and 5 ml. of the 12.5 per cent sodium carbonate solution are added. Kabat's[5] modification of the Folin-Ciocalteau procedure requires a wait for one hour at this point. However, it was found that the time can be reduced to 30 minutes if the solution is kept at 37° C. and to 15 minutes if it is kept at 80° C. After the 30 minute period 1 ml. of the Folin phenol reagent is added and the color is read after 15 minutes in a Klett-Summerson photoelectric colorimeter with filter 460. The influence of the zinc reagent on the color development was investigated and it was found that it had no influence.

Recovery of gamma globulin from pure solution. Gamma globulin dissolved in 0.6 per cent aqueous sodium chloride solution was employed as a reference standard solution. Aliquots of this solution were analyzed for

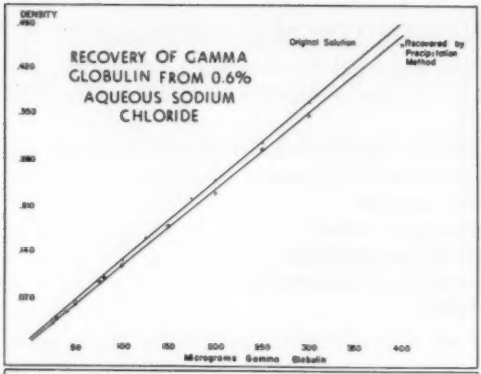


FIGURE 1.

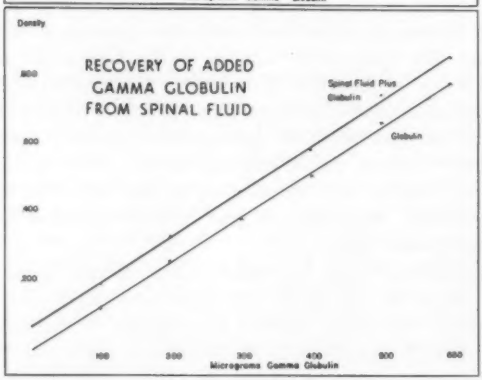


FIGURE 2.

gamma globulin by the colorimetric method both with and without precipitation by the zinc reagent. The results, presented in figure 1, show that an average recovery of 92 per cent was obtained after precipitation. The colorimetric response is linear, indicating that in the method Beer's law is obeyed.

To test further the completeness of precipitation the nitrogen content of the precipitates was determined by the micro-Kjeldahl method and the values obtained were compared with the actual amount of nitrogen present in the gamma globulin in the original aliquot of the reference solution. These values, calculated as gamma globulin, are given in table 1. From these results an average recovery of 89 per cent was obtained, confirming the fact that the precipitation is quantitative.

In order to estimate the precision of the precipitation method the gamma globulin content of 8 aliquots of the same spinal fluid was determined. The average value was 2.7 mg. per 100 ml., and the standard deviation was only $\pm$ 0.02 mg., indicating a precision of analysis of approximately 98 per cent.

TABLE 1

RECOVERY OF PRECIPITATED GLOBULIN BASED UPON NITROGEN CONTENT

Globulin used	*Nitrogen Content of Precipitate*	*Recovery as globulin*	*per cent*
1.5 mg.	0.206 mg.	1.35 mg.	90
2.0	0.268	1.76	88
3.5	0.442	2.91	83
5.0	1.017	4.40	88
7.0	1.290	6.71	95
9.0		8.52	95
		Average	89

Recovery of gamma globulin from spinal fluid. To a series of tubes containing 5 ml. of spinal fluid, aliquots of the gamma globulin solution were added containing from 100 to 500 micrograms of the globulin. The solutions were well mixed and the gamma globulin determined by the precipitation method. The results obtained are presented in figure 2. After subtraction of the value of the gamma globulin present in the spinal fluid itself from the readings of the mixture, quantitative recovery of the added gamma globulin was obtained.

Electrophoretic studies of the precipitated protein. In order to obtain information on the homogeneity of the protein precipitated from the spinal fluid, electrophoretic measurements were carried out using the Tiselius' apparatus and paper electrophoresis. Experiments with the Tiselius' method require large quantities of protein. Therefore 850 ml. of spinal fluid obtained from pneumoencephalograms was concentrated to 150 ml. by lyophilization. The protein was precipitated by the procedure previously described and redissolved in 2 ml. of 1.2 per cent aqueous sodium carbonate solution, and 10 ml. of barbital buffer pH 9.6 was added. The gamma globulin content of this solution was 0.14 per cent. Electrophoretic measurement indicated only one component with mobility of 3.06×10^{-5} cm.^{2}/volt sec. on the ascending side and 3.10×10^{-5} cm.^{2}/volt sec. on the descending side.* Paper electrophoresis in barbital buffer pH 8.6 at 220 volts for six hours indicated only one component.

RESULTS

Application of the method. The method was applied to a large number of spinal fluids, including 22 cases of multiple sclerosis. The results obtained are grouped according to increasing quantities of gamma globulin, starting with nondemyelinating neurologic diseases where the spinal fluid can be considered normal, and followed by the spinal fluids of multiple sclerotic patients. The data are presented in figure 3.

*The electrophoretic measurements were made by Dr. H. Oppenheimer of the National Cancer Institute, U. S. Public Health Service.

The average gamma globulin content and standard deviation of the spinal fluids of the multiple sclerosis patients is 12.6 ± 4.7 mg. per 100 ml., whereas the average content of the spinal fluids of non-multiple sclerosis patients is 2.0 ± 0.8 mg. per 100 ml. The difference between the averages is statistically highly significant.

The ratio of gamma globulin to the total protein content was calculated and the values are presented in figure 4. There is a significant difference between the values representing the non-demyelinating diseases and the multiple sclerosis group. However, it may be noted that among the multiple sclerotics there appears to be two kinds of abnormalities in the protein pattern. One group has a high total protein content resulting in a low ratio and another group with a low total protein content resulting in a high ratio of gamma globulin to total protein. These results may represent different phases of the disease and is a question we are pursuing further.

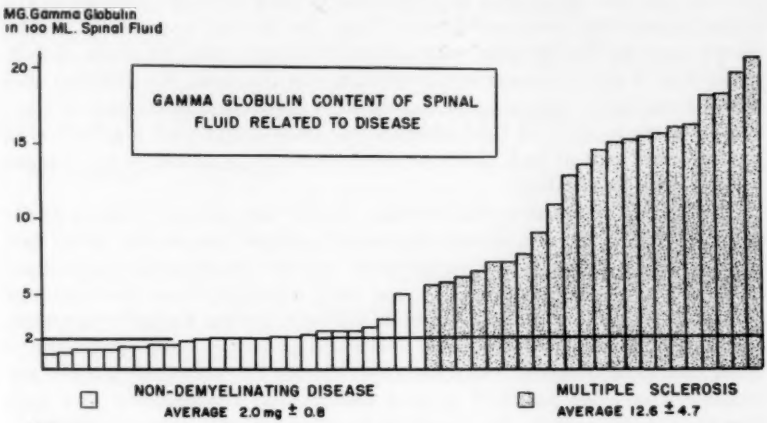
Correlation between the colloidal gold test and gamma globulin content. A generally accepted test in the diagnosis of multiple sclerosis is the colloidal gold reaction. In the 22 cases of multiple sclerosis ten gave positive tests. This ratio is about the same as that reported in the literature.[6,7] The negative colloidal gold test in so many cases of established multiple sclerosis has puzzled many investigators. We have found that in the cases where the ratio of gamma globulin to total protein is low, indicating a high content of protein other than gamma globulin, presumably albumin, the test is negative. The data on 21 cases of multiple sclerosis grouped according to high and low ratios of gamma globulin to total protein are presented in table 2.

TABLE 2

CORRELATION BETWEEN THE RATIO OF GAMMA GLOBULIN TO TOTAL PROTEIN AND THE COLLOIDAL GOLD TEST

Low ratio group			High ratio group		
Case No.	Gamma globulin content / Total protein content	Colloidal gold test	Case No.	Gamma globulin content / Total protein content	Colloidal gold test
5	7.4	Positive	16	51.0	Positive
8	7.6	Negative	19	51.7	"
15	12.0	"	31	42.0	"
18	3.4	"	32	40.0	"
35	14.0	"	37	28.0	Negative
38	9.6	"	43	36.0	Positive
40	4.8	"	53	31.0	Negative
44	9.1	"	56	20.0	Positive
50	8.2	"	73	18.0	"
51		"	74	31.0	"
			78	21.1	"

In the low group only 10 per cent of the cases gave positive colloidal gold tests, whereas in the high group 82 per cent were positive. These findings seem to support Kabat's conclusion[1] that the albumin has an inhibitory effect on the reaction between gamma globulin and colloidal gold, since it appears to



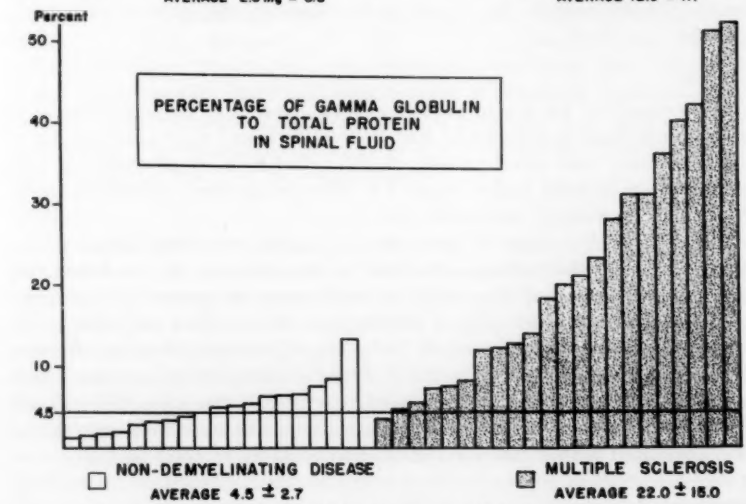


FIGURE 3 (*above*). FIGURE 4 (*below*).

reduce intensity of the color. Since albumin is more than 50 per cent of the total protein it is quite probable that in the negative cases the albumin content is high enough to inhibit completely the reaction between the gamma globulin and the colloidal gold.

In order to test this hypothesis serum albumin was added to two samples of spinal fluid from cases of multiple sclerosis with positive colloidal gold tests. The first spinal fluid contained 96 mg. per 100 ml. total protein and

19.5 mg. per 100 ml. gamma globulin, with a ratio of 20 per cent, while the second spinal fluid contained 59 and 15 mg. per 100 ml. respectively of total protein and gamma globulin with a ratio of 31 per cent. In 5 ml. of each spinal fluid 6 mg. of human serum albumin was dissolved, the colloidal gold test was run again with negative results. It is apparent that, at least in these two cases, an increase in total albumin and protein and with a reduction of ratio to 9 per cent in each case, caused the colloidal gold test to be changed from positive to negative.

Reports in the literature that children do not have gamma globulin in the spinal fluid[8] and that in a number of cases of multiple sclerosis the spinal fluid likewise does not contain gamma globulin[9] are due entirely to the inadequacy of the methods employed. Every spinal fluid, including those from children, examined by the precipitation method and also by the Kabat[10,11] immunological and electrophoretic methods contained gamma globulin. It should be noted that some diseases, which are characterized by increased vascular permeability, have an increased protein content and consequently give high gamma globulin values. In neurosyphilis, likewise, the gamma globulin is increased.

SUMMARY

A micromethod for the quantitative determination of gamma globulin in cerebrospinal fluid is described. The method is based on the separation of gamma globulin from other proteins in the spinal fluid by precipitation with zinc sulfate in barbital buffer at pH 7.3. The precipitated globulin is redissolved and determined colorimetrically.

The cerebrospinal fluids of patients with various neurologic diseases have been studied and the findings correlated to the diseases. It was found that in the group representing 22 multiple sclerosis cases the gamma globulin content is significantly higher, 12.6 $\pm$ 4.7 mg. per 100 ml., than the value of 2.0 $\pm$ 0.8 mg. per 100 ml. obtained on the group of nondemyelinating diseases. The gamma globulin findings in the multiple sclerotics were correlated with the colloidal gold test and it was found that in half the cases the colloidal gold test was negative. The negative results, with one exception, were found to be associated with a low ratio of gamma globulin to total protein.

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Quantitative Determination of Acceleration and Intracranial Pressure in Experimental Head Injury

Preliminary Report

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In most previous studies in experimental head injury where records of acceleration have been obtained, measurements have been made on the object striking the blow. Due to the error introduced resulting from deformation of the scalp, muscles, skull and striker itself, it appeared more accurate to measure the acceleration of the skull, and this procedure was followed in these experiments. The intracranial pressure produced was measured simultaneously with the measurement of the accelerations.

METHOD

The accelerometer used in these tests was the unbonded wire type, manufactured by Statham Laboratories Inc. of Beverly Hills, California. The range of the accelerometer used was ± 500 G and its natural frequency was 1600 cycles per second. The accelerations usually encountered in the experiments were such that the response of the accelerometer was linear. The accelerometer was attached to the skull on the side opposite to that on which the block was struck. It is apparent that the region of the skull directly beneath the blow would have an acceleration different from the value obtained on the opposite side, since the skull deforms markedly under the impact. The acceleration measured on the side of the skull opposite to that on which the blow is struck gives a more accurate record of the acceleration of the contents of the skull. The intracranial pressure changes were measured by means of the gage shown in figure 1. The element for recording the pressure consists of a circular diaphragm 2/1000 of an inch thick and 1/8 of an inch in diamter made of spring steel stock and having an electrical strain gage 1/16 of an inch long cemented to its center. This diaphragm is clamped at the cir-

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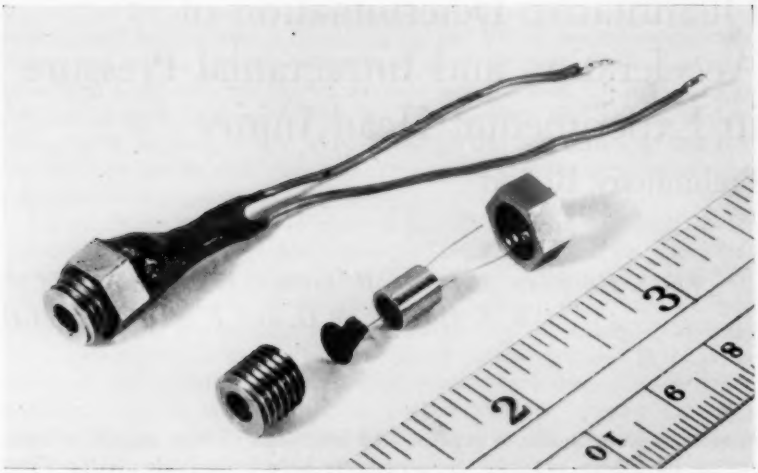

FIG. 1. Pressure gage used in this study shown both in the assembled and disassembled form. The two wires are the leads from the 1/16 inch strain gage which is cemented to the surface of the diaphragm. Changes in intracranial pressure cause deformations of this diaphragm which in turn causes deformations of the strain gage. These changes are then recorded with the aid of the oscilloscope camera.

cumference and deforms due to pressures applied to its surface, the deformations being recorded by means of the strain gage. The electrical output of the gage is a linear function of the pressure applied to the diaphragm for the range of pressures observed. The diaphragm is clamped in the end of the plug which is screwed into a tapped hole in the skull. Before inserting the plug, the dura is incised to allow cerebrospinal fluid to come in contact with the diaphragm.

Dogs of different weights were used under Nembutal anesthesia administered intravenously, one cc. of 10 per cent solution being injected per five pounds of body weight. The skull was exposed after reflection of the scalp and the temporal muscles on both sides. The accelerometer was securely attached to the skull by means of small wood screws inserted into pilot holes drilled through the bone with an electric drill. The pressure gage was mounted in a drilled and tapped hole in the skull on the same side with the accelerometer usually in the posterior parietal region about one-half inch from the midline (figure 2).

Electrical signals from both the accelerometer and the pressure gage were amplified by means of Ellis Amplifiers and then passed into a dual beam cathode ray oscilloscope. Recordings were obtained by means of a high speed oscilloscope recording camera. Ball peen hammers of various weights were used for the administration of blows on the side opposite to where the instruments were attached. The most frequently used hammer weighed 1¾ pounds.

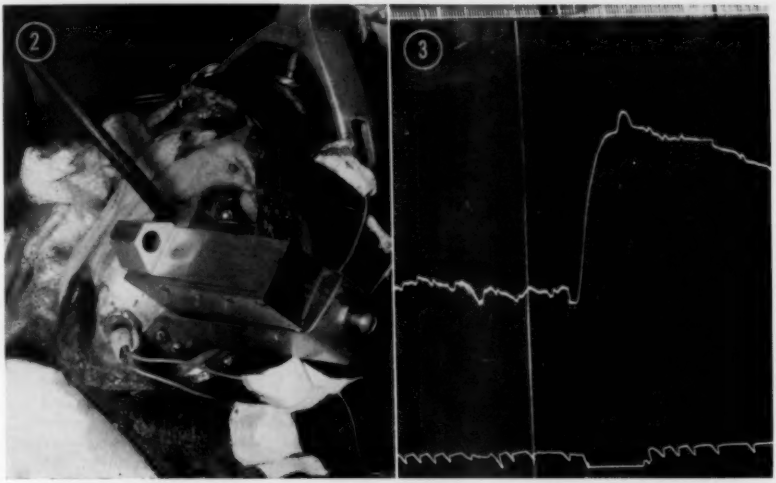

FIG. 2. Accelerometer and pressure gage in position. Note that the accelerometer is securely attached by means of wood screws inserted into the skull. The pressure gage is in a position just posterior to the accelerometer and about one half inch to the right of the midline.
FIG. 3. A concussive effect with a sudden steep rise of blood pressure (middle record) and an arrest of the respirations (lower record). In this instance the respirations returned after about 55 seconds. (upper record).

In some cases rubber pads were provided over the head of the hammer to change the acceleration given the head by the blow. The head was free to move at impact, being supported by the left hand while the right hand was used for the hammer. An attempt was made to produce a concussive effect with the first blow, but in some instances two, three and four blows were required before such an effect was obtained. The blood pressure and the respirations were recorded and a concussive effect was considered to be present only if a definite vasomotor response occurred. This reaction was characterized by a steep rise in the blood pressure with a respiratory arrest usually lasting for several seconds immediately following impact (figure 3).

RESULTS

Twenty-four experiments in which the intracranial pressure and accelerations and their time durations were measured simultaneously are reported in this preliminary study. Minimal or moderate concussive effects were obtained with accelerations varying from 250 G to over 500 G. No pattern of a relationship between severity of concussion and magnitude of acceleration could be determined from these tests. For example, a moderately severe concussion was produced in dog No. 2 for which an acceleration of 250 G was recorded. For dog No. 7 an acceleration of 500 G was associated with a minimal or

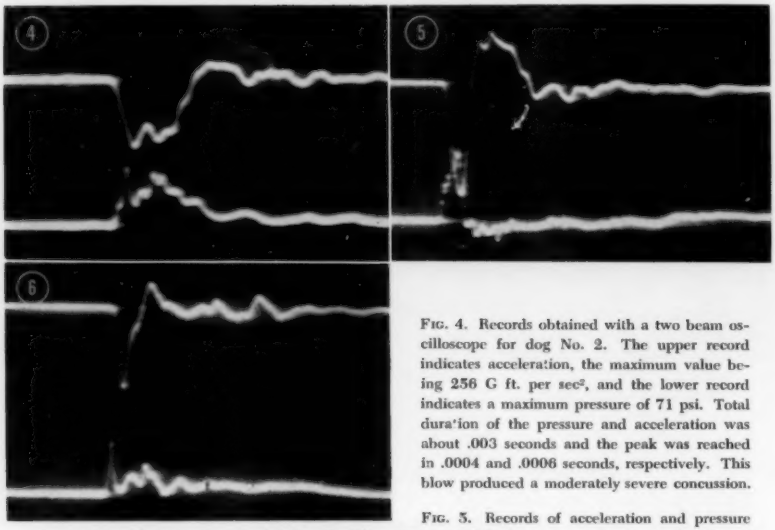

FIG. 4. Records obtained with a two beam oscilloscope for dog No. 2. The upper record indicates acceleration, the maximum value being 256 G ft. per sec^2, and the lower record indicates a maximum pressure of 71 psi. Total duration of the pressure and acceleration was about .003 seconds and the peak was reached in .0004 and .0006 seconds, respectively. This blow produced a moderately severe concussion.

FIG. 5. Records of acceleration and pressure associated with concussion in dog No. 7. The upper record indicates a maximum acceleration of 500 G ft. per sec^2 and the lower record indicates a maximum pressure of 60 psi. The total duration of both pressure and acceleration was about 0.001 seconds.

FIG. 6. Records of acceleration and pressure obtained in the case of dog No. 20 in which no concussion was produced. The maximum acceleration reached was 370 G ft. per sec^2 and the maximum pressure was 40 psi. The acceleration lasted .001 seconds and the pressure .002 seconds.

threshold concussive effect and for dog No. 20 no concussion was produced by a blow resulting in an acceleration of 370 G.

The study of the intracranial pressure change at the time of impact in these experiments suggests that the time duration of the pressure increase is most significant rather than the maximum levels obtained. For dog No. 2 the intracranial pressure at a point opposite the blow was 70 psi, for dog No. 7 the pressure was 60 psi, and for dog No. 20 it was 40 psi. The pressure and acceleration in dog No. 2 lasted 3/1000 of a second and in dog No. 7 1/1000 of a second; in dog No. 20 the time duration of the pressure was 1/2000 of a second while the acceleration lasted about 1/1000 of a second. In the accompanying figures 4, 5 and 6 one can compare the time duration of acceleration and intracranial pressure change. In dog No. 22 a concussion similar to that produced in dog No. 2 was obtained. In this animal the acceleration as shown in figure 7 was well over 500 G and lasted 1/1000 of a second while the pressure was 70 psi and lasted 2/1000 of a second. Although the acceleration was much higher than in dog No. 2, the pressure and its duration were similar for both dogs. (While the accelerometer was calibrated to 500 G it did not reach the stop until an indication of 800 G was given.) For dog No. 22 a rough estimate of the actual acceleration was 650 G.

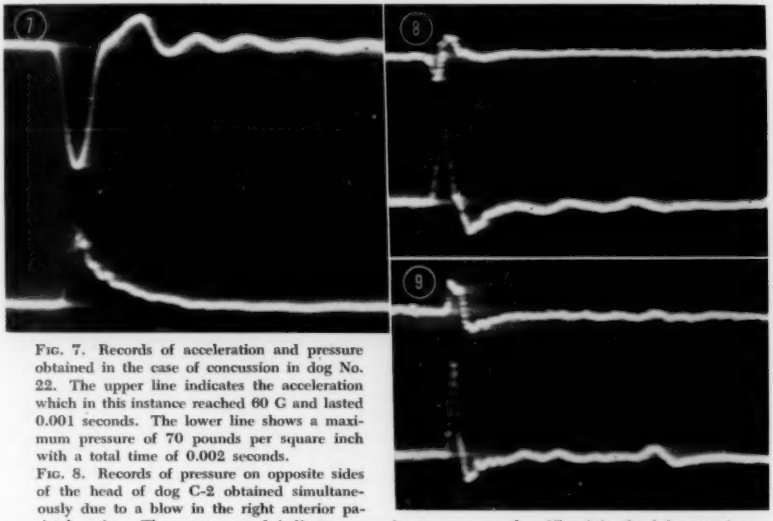

FIG. 7. Records of acceleration and pressure obtained in the case of concussion in dog No. 22. The upper line indicates the acceleration which in this instance reached 60 G and lasted 0.001 seconds. The lower line shows a maximum pressure of 70 pounds per square inch with a total time of 0.002 seconds.

FIG. 8. Records of pressure on opposite sides of the head of dog C-2 obtained simultaneously due to a blow in the right anterior parietal region. The upper record indicates a maximum pressure of —17 psi in the left posterior parietal region and the lower record indicates a maximum pressure of +45 psi in the right posterior parietal region.

FIG. 9. Bilateral pressure records of dog F-2 obtained with a blow to the right anterior parietal region. The upper record indicates a maximum pressure of +18 psi in the left posterior parietal region and the lower record indicates a maximum pressure of +30 psi in the right anterior parietal region.

Increase in intracranial pressure at the time of the impact, in a head that is permitted to move, is produced by two separate causes: the first being due to deformation of the skull and the second being due to acceleration or the sudden setting of the head to motion. The inbending of the skull results in compression of the contents in a more or less uniform manner producing uniform pressure increases throughout. An increase in pressure from acceleration, or setting of the head to motion suddenly, is associated with an increase in intracranial pressure on the side of the blow and a drop in pressure on the opposite side. The drop in pressure on the opposite side is due to compression and lagging of the contents of the skull. If the deformation of the skull due to the blow is slight and the head is free to move, the negative pressure on the opposite side can be measured. This is illustrated in the record obtained in dog C-2 (figure 8) in which pressure gages were applied on both sides of the skull. With a blow in the right anterior parietal region, the pressure on the same side as the blow was 45 psi while the pressure on the opposite side was —17 psi. The record obtained from dog F-2 (figure 9) indicates a condition where a deformation of the skull is severe enough to result in positive pressure throughout. In this dog with a blow in the right anterior parietal area the pressure on the same side as the blow was 30 psi and on the opposite

TABLE 1.

ACCELERATION AND INTRACRANIAL PRESSURE IN EXPERIMENTAL HEAD INJURY

Animal No.	*No. of blows*	*Peak pressure opposite blow* (psi)	*Total pressure duration* (sec.)	*Peak acceleration* ft./sec.2	*Total acceleration duration* (seconds)	*Physiological response* (degree of concussion)	*At blow number*	*Remarks* (type of fracture)
1	4			390 G	0.0005	Severe	4	No fracture
2	1	70	0.003	250 G	0.003	Moderate	1	Circular comminuted
3	4			300 G		None	4	No fracture
4	3	+10 —55		310 G		Concussion	3	Linear
5	5	—60		460 G		Minimal	3	Linear
6	1					Severe	1	Linear
7	2	60	0.001	500 G	0.001	Minimal	2	No fracture
8	1	25		470 G		Concussion	1	Comminuted
9	2	25	0.0005	390 G	0.001	Minimal	2	Linear
10	1	75	0.0005	Est. 680 G	0.0005	Concussion	1	Comminuted
11	1	85		380 G		None	1	Comminuted
12	2	95		410 G		Minimal	2	Comminuted
13	1	95	0.0005	190 G	0.0015	None	1	Linear
14	3	65	0.002	260 G	0.0005	Fatal	3	Comminuted
15	1	60	0.006	390 G	0.0015	Fatal	1	Comminuted
16	3	80	0.001	Est. 530 G	0.001	Moderate	1	No fracture
17	1	65	0.0005	230 G	0.001	None	1	Linear
18	1	55	0.001	270 G	0.0005	Severe	1	Linear
19	3	10	0.0005	Est. 750 G	0.001	None	3	Linear
20	1	40	0.0005	370 G	0.001	None	1	Linear
21	1	—45	0.003	Est. 780 G	0.001	Minimal	1	Linear
22	2	70	0.002	Est. 650 G	0.001	Moderate	2	Comminuted
23	1	85	0.005	Est. 650 G	0.0005	Severe	1	Slight depressed
24	2	75	0.004			Severe	2	Extensive depressed

Blanks in the table indicate data were not obtained. Maximum transverse distance through the skull varied from 1.96 inches to 2.20 inches. Pressure gage was placed in the posterior parietal region about ½ inch from the midline. The accelerometer was placed on the same side as the pressure gage and this was almost always on the right side. It should be noted that the total duration of the pressure and the acceleration signifies the period from the beginning of the pressure or the acceleration to the end on the record. It does not signify that the total pressure duration or the total acceleration duration was of the peak pressure or acceleration given in column 3 and 5. Negative pressures as noted imply the force necessary to move the skull contents away from the pressure plug in contradistinction to a movement of the contents toward the plug which would be recorded as positive pressure.

side 18 psi. It is interesting to note that these animals were not concussed, and again the time duration of the increased intracranial pressure appears to be significant. Pressure durations here are of the order of 1/2000 to 1/2500 of a second.

In most of the experiments performed by striking the skull with a hammer, it was found that the skull deformation was so great that the pressure due to the deformation was of primary significance and positive pressures were generally measured opposite the point of the blow as well as on the same side with a blow. The magnitude of the pressure levels reached in these experiments might better be appreciated if it is pointed out that 50 pounds per square inch corresponds approximately to 2600 mm. Hg.

CONCLUSION

Concussive effects were produced by blows resulting in accelerations of 250 G to over 500 G. The intracranial pressure rise measured at the same time ranged from 25 to 95 psi. Concussions of minimal, moderate and severe degree were obtained.

The time duration of the pressure and the acceleration appeared to be the significant single factor which explained the clinical effects following impact. It was noted that at the lower values of pressure and acceleration a concussion was produced only if the duration of the acceleration and pressure was of an appreciable length. For the higher accelerations and pressures, it was apparently not necessary that they last for as long a time to produce concussion.

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Of all the immediate causes of epilepsy the most potent are psychical – fright, excitement, anxiety. To these were ascribed 157 cases, more than one-third of those in which a cause was given, and one-seventh of the whole series. Of the three forms of emotion, fright takes the first place with 119 cases, 10 per cent of the whole. The relation of this cause to age is, however, very distinct. It is effective chiefly in early life, when emotion is so readily excited, and is most powerful at the transition from childhood to adult life, while after middle life it is almost inactive. Of the 119 cases only 3 commenced after thirty years of age, and 100 commenced under twenty. Of these, the majority, 70, commenced between ten and twenty, only 30 cases under ten. The female sex is notoriously the more emotional, and accordingly the disease, as Sieveking and others have pointed out, results from fright in a larger proportion of females than of males, although the difference is, perhaps, less than might be expected – 71 females and 48 males; 60 and 40 per cent respectively. It is notorious also that the difference between the sexes in emotionality increases as life advances. In childhood one sex is almost as emotional as the other, but with puberty men become far less emotional than women. The influence of fright as a cause of epilepsy is in strict harmony with this fact. Under ten years of age the sexes suffer equally. Between ten and twenty the males are to the females as 3 to 4; between twenty and thirty as 3 to 13, and over thirty the only cases due to this cause occurred in women. After seventeen, only 3 cases occurred in men, while 20 occurred in women.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Muscle Action Potentials in Polymyositis

*Fritz Buchthal, M.D. and Paolo Pinelli, M.D.**

THE recent description of virus infections similar in symptomatology to poliomyelitis,[1,2,3] but characterized by extensive lesions in skeletal muscle, has aroused new interest in the study of inflammatory reactions of skeletal muscle. Primary inflammatory processes have been described in polymyositis and dermatomyositis (the literature on this subject has recently been reviewed).[4] In a number of myopathies, inflammation may occur secondarily, e. g. in progressive muscular dystrophy and myasthenia.

It is well known that the clinical diagnosis of the subacute and chronic phases of polymyositis can be extremely difficult since symptoms are nonspecific, and in a number of cases there is not the characteristic involvement of the skin. Therefore, the diagnosis must be based on muscle biopsy. Microscopic examination reveals the presence of lymphocytes, histiocytes, in severe cases of polynucleocytes, and sometimes eosinophilic cells infiltrating the interstitial tissue of the muscle and surrounding the individual muscle fibers. The degree of atrophy varies according to the duration and severity of the disease. In most cases, inflammation is patchy, with localized foci of atrophic tissue (nodular polymyositis[5]). The inflammatory process can either persist for several years or, unless regeneration occurs, result in dystrophic changes histologically indistinguishable from progressive muscular dystrophy.[4]

The mean duration of muscle action potentials has been used to differentiate between atrophies of neurogenic and of myogenic origin. In atrophies caused by affection of the lower motor neuron, the mean duration of the muscle action potentials was found to be considerably increased,[6] while in muscular dystrophies a decrease has been described.[7]

It is the aim of the present study to investigate muscle action potentials in polymyositis with respect to mean duration, shape and amplitude. It was thought possible that such a study might contribute to our knowledge of the etiology of dystrophic changes in muscle in view of the fact that, in our experience,[8] patients with genuine muscular dystrophy do not always show the changes in mean duration of action potentials described as typical.[7]

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*Working with a fellowship from the Rask-Örsted Foundation.

The work was supported by grants from the Danish Association for Infantile Paralysis and the Michaelsen Foundation.

METHOD AND MATERIALS*

The subjects were eight males and three females, hospitalized within a one year period in the Rigshospital, Copenhagen, with an established diagnosis of polymyositis. The age of the patients ranged from seven to 48 years, with approximately half under and half over 20 years: two were under nine years and three were in the second decade; two were in the third, one in the fourth, and three patients were between 40 and 48 years of age.

Since polymyositis is such a poorly defined entity, the diagnosis was established histologically in each case, often by repeated biopsies, and specifically in those muscles investigated electromyographically.**

In all cases, action potentials were led off with three different types of electrodes: 1) a unipolar electrode (0.8 mm. diameter) thoroughly insulated except for an area of 25 to 100 μ in diameter at the tip; 2) a concentric needle electrode consisting of an insulated platinum wire (0.1 mm. diameter) in a steel cannula of 0.9 mm. diameter with a leading off area for the central electrode of 10^4 μ^2; 3) a bipolar needle electrode consisting of two insulated platinum wires, each 0.1 mm. in diameter, in a steel cannula of 0.9 mm. in diameter. When using the unipolar electrode, a 1 x 1 cm. metal plate served as indifferent electrode and was fixed on the skin near the point of insertion of the different electrode, the skin resistance being reduced by the use of electrode paste. The patient was grounded by a special plate electrode.

All values from pathologic muscles were compared with values obtained with the same electrode from corresponding muscles of normal subjects of the same age. With each electrode, at least 120 action potentials were recorded from normal muscles under standardized conditions. Fifty-five action potentials on the average were recorded during slight voluntary effort from each pathologic muscle.

Action potentials were led off simultaneously from two regions of the same muscle. The potentials were ampilfied maximally 10^5 times by two differential amplifiers whose output was connected to the d.c. amplifiers of a Dumont double beam oscilloscope (type 279). The overall amplification was 3 db. down at 0.5 and at 3000 c.p.s. The action potentials were recorded photographically using single or continuous sweep, and each potential was photographed three times. When using single sweep, the film was moved at low velocity (five cm. per sec.) and the sweeps initiated at a rate of 3 per sec. By this procedure, subsequent sweeps were separated, and it was possible to spread out and record isolated action potentials at moderate recording velocity. Since the film moved during the sweep time, the angle between the y-axis and the x-axis was $> 90°$ and the coordinate system was oblique. Calibration with respect to amplification and sweep velocity was performed by

*This detailed description of the method and of the statistical evaluation of results applies also to following communications on the same subject.

**The histologic examinations were kindly performed by Erna Christensen, M.D., of the laboratory of neuropathology, Institute of Pathology, University of Copenhagen.

a laboratory generator with calibrated output.

For measurement, the recorded action potentials were enlarged approximately seven times by projection and the total duration and amplitude were measured. In view of the fact that leading off from fibers within a muscle corresponds to measuring from a volume conductor, the total duration of the action potentials was found to be a more accurate expression of the electrical response of the muscle[9] than the negative spike of the triphasic potentials only.[10]

It has been shown previously that both duration and amplitude of the action potential vary with temperature.[9,11,12] For this reason, the intramuscular temperature was recorded with a thermocouple and kept constant at 36° C. when necessary by means of a heating pad placed over the muscle.

Apart from the analysis of the individual action potentials, the activity of the muscle was estimated from the electromyogram recorded at slow velocity (5 cm./sec.) and at maximum effort. The electromyograms were classified as showing a pattern of interference activity (I), single or isolated action potentials from the subunit* nearest the electrode (S), or a transitory state (T) in which single action potentials could be discriminated in spite of a relatively pronounced background activity. It was found previously[6] that in the majority of cases of diffuse myogenic atrophy, maximum voluntary effort was associated with interference or transitory patterns, whereas, even at maximum effort, only isolated action potentials could be recorded in the patchy atrophies of neurogenic origin. In the present series of polymyositis cases, maximum effort was associated with a pattern of interfering activity in all instances.

The clinical degree of atrophy was estimated as slight, medium or severe. Muscle power was estimated with the muscle acting as "fixator" during maximal effort, and classified as follows:[13]

1 = flicker or trace of contraction.
2 = active movement with gravity eliminated.
3 = active movement against gravity.
4 = active movement against gravity and resistance.
5 = normal power.

In the present cases the muscle power fell within groups 3 to 5.

STATISTICAL EVALUATION

The mean values for action potential duration and amplitude in polymyositic muscles were compared with values recorded with the same electrode from corresponding muscles of normal subjects of the same age. The results are presented in distribution curves for the different groups of patients and for normals. The histograms of duration do not correspond with a Gaussian distribution either in normal or in dystrophic muscle. The distributions are oblique with the ascending part of the curve, especially in dystrophic muscle,

*Subunit denotes adjacent muscle fibers belonging to the same motor unit and giving rise to the "motor unit potential." [9]

TABLE 1

LIMITS FOR STATISTICALLY SIGNIFICANT CHANGES IN MEAN DURATION FOR DIFFERENT NUMBERS OF ACTION POTENTIALS AND DIFFERENT STANDARD DEVIATIONS

Standard Deviation	*Number of Action Potentials*				
	10	20	30	40	50
	Statistically Significant Percentage Change				
2 msec.	27	19	16	14	12.5
2.5—	33	24	19	17	15.5
3 —	40	28	23	20	18
3.5—	46	33	27	23.5	21
4 —	53	37.5	31	27	24

The changes are expressed in per cent of values in normal muscle with a mean duration of 6 msec., a standard deviation of 2 msec. and a mean error of 0.1 msec.

being steeper than the descending which represents action potentials of long duration. However, the deviation from a symmetrical distribution is not so marked that a Gaussian function could not serve as a suitable basis for the statistical estimation.

The statistical analysis was based on the calculation of the mean value (m), the standard deviation (δ) and the mean error (ε), defined as:

$$\delta = \sqrt{\frac{\Sigma(x-m)^2}{N-1}} \qquad \text{and} \qquad \varepsilon = \frac{\delta}{\sqrt{N}}$$

where x denotes the individual value of the quantity measured and N is the total number of measurements. The mean value was determined arithmetically and graphically from the distribution function. The difference between these two mean values was only slight (< 10 per cent) and was due to the asymmetry in distribution.

The statistical significance of a difference in mean duration was estimated from the value of

$$\eta = \frac{m_n - m_d}{\sqrt{\varepsilon_n^2 + \varepsilon_d^2}}$$

where m_n and m_d denote the mean values and ε_n and ε_d the mean error in normals and in patients, respectively. In the present material, $\eta \geqq 2.5$ is considered to indicate a statistically significant difference. In a Gaussian distribution, there is a probability of only one per cent that two determinations of the mean value will give a difference more than two and a half times the mean error. Therefore, the value of 2.5 for η indicates a 99 per cent probability that the difference observed is real. Considering the asymmetry of the present distribution function, the probability is reduced but is certainly not below 95 per cent. The minimum change in action potential duration which is statistically significant for a given number of action potentials – i. e. the change for which $\eta = 2.5$ – is given in table 1. Since the number of action

TABLE 2

ATROPHY, ACTIVITY, DURATION OF DISEASE, BIOPSY FINDINGS AND MUSCLE ACTION POTENTIAL DURATION IN POLYMYOSITIS

Subjects	*Age*	*Duration of disease*	*Muscle examined*	*Degree of atrophy*	*Degree of activity*	*Change in mean duration in per cent of normal value*	*Measure of statistical significance*	*Microscopic examination: Degree of inflammatory reaction*	*Microscopic examination: Degree of atrophy*	*Microscopic examination: Degree of proliferation of connective tissue*	*Microscopic examination: Distribution of changes*
1. E.S.P. female	26	4 years	biceps brachii sin.	slight	4	−37	4	+	(+)	(+)	nodular
2. A.M.T.H. female	16	6 months	biceps brachii sin.	medium	4	−50	9	+++	++	+	diffuse
3. I.P.C. male	41	7 years	triceps brachii dxt.	medium	3-4	−31	5	++	+++	+	nodular
4. H.H. male	8	6 years	biceps brachii sin.	medium	4	−28	5	+(+)	(+)	+	diffuse
		7 years	biceps brachii sin.	medium	3-4	−53	8	++	++	++	diffuse
		6 years	gastrocnemius dext.	medium	4	−23	10	+	(+)	0	nodular
		7 years	biceps brachii dext.	medium	3	−55	3	++(+)	++	++	nodular
5. T.R. male	16	9 years	biceps brachii dext.	medium	3	−23	3	+	(+)	++	nodular
6. A.S.C. male	15	9 years	biceps brachii dext.	medium	3	−45	6	+	+	+(+)	nodular
7. A.R.N. male	44	6 months	supraspinatus dext.	medium	2-3	−52	4	+	+	0	diffuse
8. I.V. male	29	4 months	supraspinatus sin.	slight	4	−60	6	+	+	(+)	nod
9. M.E.K.	7	2 years	erector spinalis dext.	slight	3	−43	5	+	+	+	diffuse
male		2 years	rectus femoris sin.	slight	3-4	− 7	1	+	+	+	nodular
10. H.B.K.	48	2 years	biceps brachii sin.	slight	4	−41	5	(+)	(+)	0	diffuse
male		2 years	deltoideus sin.	slight	4	−18	2	(+)	0	0	nodular
11. G.K.G. female	35	2 years	rectus femoris dext.	slight	3-4	−17	2.8	+	(+)	++	nodular

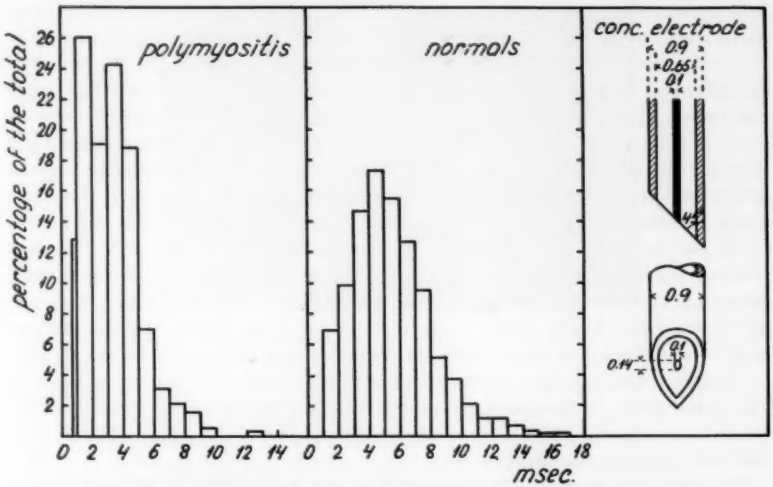

FIG. 1. Histogram of action potential duration in polymyositic and normal muscle recorded with the concentric electrode illustrated to the right. Total number of action potentials in polymyositic muscle: 179. Total number of action potentials in normal muscle: 507.

potentials obtainable from a muscle is limited and variable, these figures make it possible to decide whether changes in duration are significant or not.

The distribution curves of action potential amplitude are considerably more asymmetric than are those of duration, since the distance between electrode and active region influences measurements of amplitude more than duration. Therefore, criteria for significant differences are more difficult to define and only large increases (> 100 per cent) were considered significant.

RESULTS

1. *Action potential duration.*

The main feature of the action potential in polymyositis was a considerable *decrease in mean duration* (figure 1). This decrease averaged 35 per cent when all potentials were considered, and 40 per cent when the 8 per cent polyphasic potentials (> 4 phases) were excluded from the calculation. An obvious inflammatory response was present in all muscles (table 2). There was a clear correlation between decrease in mean action potential duration and the occurrence of inflammation. Since a biopsy sample is not necessarily representative of the conditions in the muscle as a whole, a certain correlation in degree between inflammation and the decrease in action potential duration could hardly be expected. It is true that patients with mild pathologic changes averaged a decrease in mean duration of 34 per cent against 44 per cent for patients with severe pathologic involvement. Similarly, patients with nodular lesions averaged a decrease in mean duration of 32 per

cent against 45 per cent for patients with diffuse involvement (table 2). Thus, there seems to be a trend, but the figures are not statistically significant.

Aside from this correlation between decrease in mean action potential duration and occurrence of an inflammatory reaction, other correlations were not found. The changes in action potential duration were evident even in cases in which the atrophy was slight. There was no significant correlation between the degree of atrophy as revealed by microscopic or clinical investigation and the mean duration of the action potentials (table 2). Thus, the mean duration in the presence of medium and severe atrophy was decreased by 42 per cent, and in the presence of slight atrophy by 43 per cent. No correlation could be found between the decrease in duration of the action potentials and the duration of the disease (table 2). Cases with a duration up to two years had a mean decrease of 44 per cent; over two years, 42 per cent. The decrease in action potential duration was not related to sex or age.

Unipolar and bipolar electrodes gave similar results, as shown in table 3. This table gives, furthermore, the standard deviation, the mean error and the measure of statistical significance of the differences in duration between normal and polymyositic muscle.

The various aspects of the investigation are exemplified in figure 2 which contains a muscle section, the electromyogram at maximum effort and the distribution curve of action potential duration for a representative case.

Activity in apparently relaxed muscles was observed in two cases (eight and nine of table 2), but can hardly be considered as characteristic for polymyositis. In case nine, it could be expected on account of the myotonic reaction in the muscle investigated.[14] In this case, mean action potential duration differed strikingly in the two muscles examined. In the rectus femoris the values were normal, and biopsy showed an extremely localized distribution of inflammatory changes, combined with a degeneration of muscle fibers in the affected areas so complete as to be incompatible with function. The fibers of the spinal erector muscle showed, by contrast, diffuse infiltration, a minor degree of degeneration and a significant decrease in mean duration of the action potentials.

2. *Action potential amplitude*

In normal muscle, action potential amplitudes vary over a wide range, mainly due to variations in the distance between generator and electrode. The distribution of amplitudes in polymyositic muscles did not differ significantly from normal. It is true that a decrease in the action potential amplitude was found in some muscles when recording with the bipolar electrode, but this did not occur in the majority of muscles investigated, and neither the unipolar nor the concentric electrode gave potential amplitudes which deviated significantly from normal (table 3).

3. *Shape of action potentials*

The various shapes of action potentials are illustrated in figure 4, and their distribution in polymyositic and in normal muscles, as obtained with

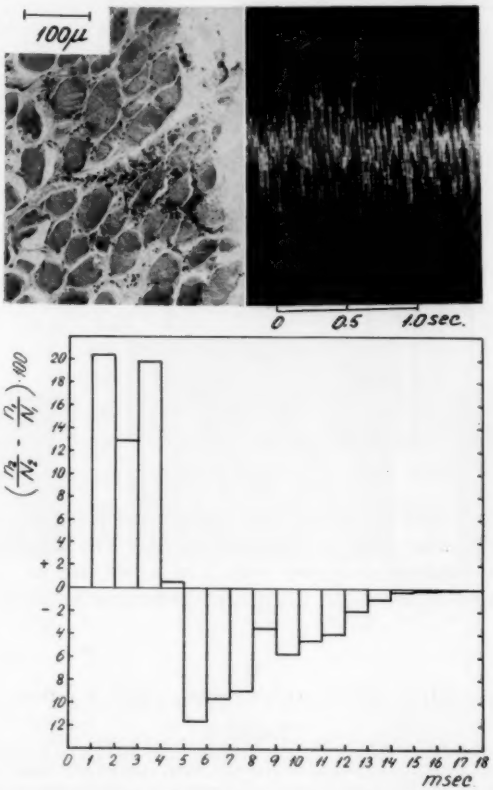

FIG. 2. H.H., male, 8 years, clinical diagnosis: polymyositis; diffuse slight atrophy and pain in arms and legs; no specific localization of atrophy to the shoulder girdle. *Left:* Microphotograph of muscle tissue (biceps brachii sin.) showing infiltration. *Right:* Electromyogram showing pattern of interfering activity at maximal effort. *Below:* Distribution curve of action potential durations expressed as the difference between the distribution for polymyositic and normal muscle. Columns above the line indicate the percentage increase in short action potentials in polymyositic as compared with normal muscle; columns below the line indicate the corresponding decrease in long action potentials. Mean action potential duration 40 per cent less than in normal muscle.

$N_1 = 1177$ (total number of action potentials from normal muscle).

n_1 : number of action potentials for each interval of duration in normal muscle.

$N_2 = 52$ (total number of action potentials from the polymyositic muscle).

n_2 : number of action potentials for each interval of duration in the polymyositic muscle.

the concentric electrode, is compared in figure 3. Diphasic potentials of short duration (figure 4a) increased to 67 per cent in polymyositic as compared with 46 per cent in normal muscles, while the occurrence of triphasic potentials (figure 4c) was almost correspondingly decreased. Similar results were obtained with bipolar and unipolar electrodes. With all three electrodes,

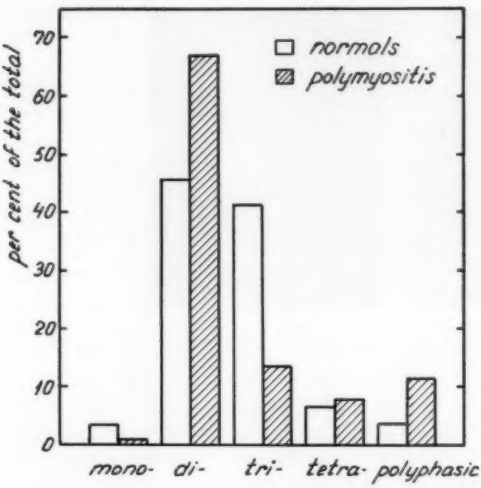

FIG. 3. Distribution of different shapes of muscle action potentials in normal (692 action potentials) and polymyositic muscle (142 action potentials), obtained with the concentric electrode, dimensions see figure 1.

there was an increased appearance of irregular and polyphasic action potentials of more than four phases (figures 4e and 4f). The latter averaged 8 per cent of all potentials as compared with 1 to 3 per cent in normal muscle. With the concentric electrode, polyphasic potentials averaged 12 per cent (figure 3).

DISCUSSION

In a disease such as chronic polymyositis, which is rather non-specific in

TABLE 3

MEAN ACTION POTENTIAL DURATION, AMPLITUDE AND STATISTICAL EVALUATION FOR NORMAL AND POLYMYOSITIC MUSCLES RECORDED WITH DIFFERENT TYPES OF ELECTRODES

Electrodes	DURATION								
	*Mean duration**		*Number of action potentials*		*Standard deviation*		*Mean error*		*Measure of statistical significance*
	norm.	*polymyo.*	*norm.*	*polymyo.*	*norm.*	*polymyo.*	*norm.*	*polymyo.*	
Concentric	5.4	3.2	507	179	2.1	1.4	0.03	0.11	17.1
Unipolar	5.9	3.4	653	120	2.0	1.4	0.08	0.13	16.6
Bipolar	4.3	2.3	526	378	1.5	1.3	0.07	0.06	21.0

Electrodes	AMPLITUDE								
	Mean amplitude		*Number of action potentials*		*Standard deviation*		*Mean error*		*Measure of statistical significance*
	norm.	*polymyo.*	*norm.*	*polymyo.*	*norm.*	*polymyo.*	*norm.*	*polymyo.*	
Concentric	185	193	507	179	140	126	6.2	9.3	0.7
Unipolar	248	261	653	120	136	128	5.3	11.7	1.0
Bipolar	197	128	524	378	110	105	4.8	5.8	9.2

*The 8 per cent polyphasic potentials are not included in the calculations.

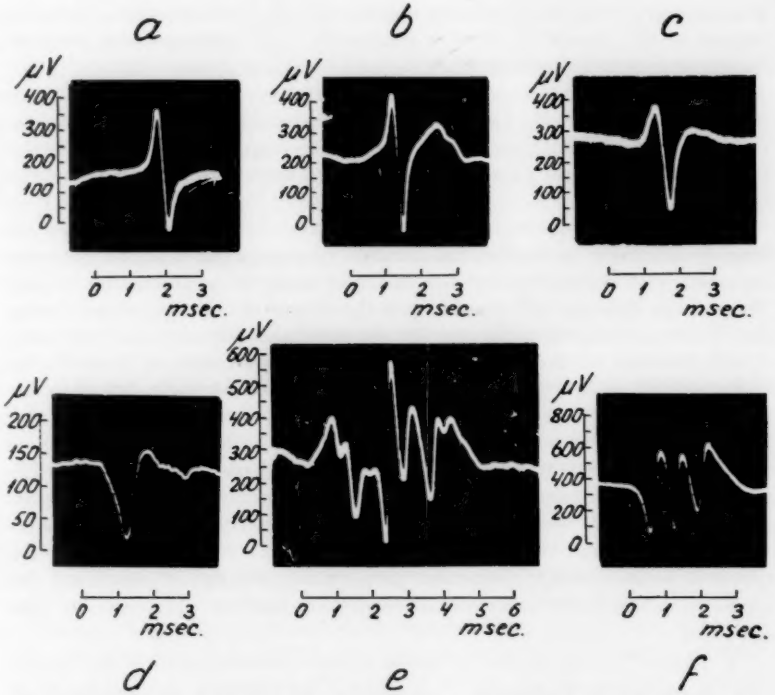

FIG. 4. Different types of action potentials recorded with the concentric electrode in polymyositic muscles during voluntary effort. (*a*) regular diphasic potential; (*b*) and (*c*) triphasic potentials; (*d*) almost monophasic action potential; (*e*) polyphasic potential, consisting of a group of potentials; (*f*) polyphasic potential consisting of a series of spikes of shorter duration than in (*e*).

its clinical symptomatology, the constant finding of a decrease in the mean action potential duration is of considerable diagnostic value. This finding is much more consistent than in progressive muscular dystrophy.[8] Contrariwise, histologic dystrophic changes and clinical atrophy and paresis were slight in polymyositis as compared with dystrophy. It is the inflammatory aspect of the pathologic process which is significantly correlated, in polymyositis, with the decrease in mean action potential duration. The reduction in mean duration is found in the acute stage of polymyositis in Coxsackie-infected mice as well.[15]

In evaluating changes in action potential duration, it is important to emphasize that a decrease is not confined to pathologic conditions. In all normal muscles, there is a considerable percentage of action potentials shorter than 4 msec., the percentage being 36 for the concentric electrode. For this reason

it is necessary to record a sufficient number of action potentials from different regions of the muscle to allow a statistically valid differentiation between normal and pathologic states.

The cause of the decrease in mean duration of the action potentials in polymyositis can only be discussed on a somewhat speculative basis. In general, differenecs in duration can be due to differences in the mean distance between electrode and generator and to differences in the properties of the subunit.

Considering that leading off from inside the muscle corresponds to conditions in a volume conductor, the duration of the recorded action potential decreases with decreasing distance between electrode and potential source. The average distance will depend upon the degree of activity present during the recording, i. e., upon the number of simultaneously activated subunits; it will decrease when many different action potentials arise in a small area of the muscle. However, at the same time the mean amplitude should be increased. As this was not the case, this explanation can be discarded as the cause of the reduction in mean duration in polymyositis.

For the same reason, a more coincident summation of potentials from different fibers of the subunit cannot be responsible for the increased occurrence of action potentials of short duration. If an increased conductivity of interstitial fluid, as it might arise around the fibers, were responsible for the decrease in mean duration (increased propagation velocity), a significant decrease in action potential amplitude would be expected. This was, in fact, not found.

A decrease in the number of active muscle fibers composing the "motor unit," according to Kugelberg,[7,16] diminishes the duration and amplitude of the action potential and modifies its shape. The reduction in number of fibers is considered by him to be the cause of the decrease in mean duration. In our experience,[8] however, there is no close correlation between fiber loss and mean action potential duration. For instance, in dystrophy[8] the same degree of atrophy might or might not be associated with a decrease in mean duration. In polymyositis, on the other hand, in which a pronounced decrease in mean action potential duration is a constant finding, the degree of atrophy in most cases was slight and the dystrophy, though present, was not nearly as pronounced as in muscular dystrophy.

Theoretically, loss of fibers within a subunit may either show a scattered random distribution or may occur selectively. *Random loss* should be associated with a considerable increase in irregularly shaped and polyphasic potentials. Actually in polymyositis the observed decrease in mean duration was mainly attributable to a relative increase in the number of regular diphasic potentials of short duration.

The observed change in action potential duration could be accounted for if one assumes a *selective loss of fibers,* i. e., a loss of those fibers whose action

potentials contribute mainly to the first or to the terminal portion of the summated subunit potential.

One can only speculate as to the basis on which such a selective fiber loss might occur. The two possibilities that come to mind are related (a) to properties of the muscle fibers and (b) to properties of nerve and end plates.

Selective loss may occur on the basis of the propagation velocity of the impulse over the muscle fiber. Short action potential durations would then result from loss of function of muscle fibers with either high or low conduction velocity. This explanation, however, cannot cover the finding of a large increase in regular disphasic potentials of short duration. The other possibility for obtaining short potential duration by selective loss concerns the spatial distribution of the motor end plates. In general adjacent motor end plates must be activated simultaneously. If a number of adjacent end plates were blocked in polymyositis, the temporal dispersion of the summated subunit potential would be reduced. There is, however, no other evidence for end plate or nerve affection in polymyositis and the assumption of selective loss on the basis of a block of adjacent end plates seems unlikely.

Finally one must consider changes in the muscle fibers. The increased occurrence of diphasic potentials requires an assumption that the functional length of the fibers has been reduced. This could result from destruction of the fiber ends or from external short circuits (shunts) produced e. g. by localization of the inflammatory process to the end of the fibers. These assumptions have not yet been verified histologically because of the difficulties in obtaining biopsy specimens of whole muscle. Since triphasic action potentials with more than three phases were shortened as well, one must in addition assume a general increase in propagation velocity of the impulse over the muscle fibers.

SUMMARY

In 11 cases of histologically verified polymyositis, the mean duration of muscle action potentials showed a statistically significant decrease of up to 60 per cent as compared with normal muscle from subjects of the same age (figure 1). There was an increased occurrence of diphasic action potentials of short duration (figure 3). This decrease in mean duration was attributable to the inflammatory aspect of the pathologic process. The factors are discussed which might account for these changes in the distribution of duration and shape. It seemed most likely that they could be accounted for on the basis of a general increase in propagation velocity of the impulse over the muscle fiber combined with a reduction in the functional length of the fiber.

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Emotional disturbance is another very frequent exciting cause of the megrim paroxysms, certainly no less so than gastric disorder. Unfortunately, as Dr. Latham has truly said in the parallel case of Angina pectoris, "the will is far less master of the mind than of the body. A man may resolve never to move from his chair, but he cannot resolve never to be angry." It is, of course, quite impossible for any one to avoid the circumstances which call forth emotional feeling, but it is no less certain that the development of our passions and their reaction on the bodily functions, may be very much heightened or subdued by force of habit. A man cannot alter his natural temperament, and the best resolution never to be angry, grieved, or anxious, would certainly fail, nor would it be desirable that it should be otherwise; but there is such a thing as "giving away" to tempers and "nursing" griefs and fears; and in proportion as this is done, so will they become organized in our constitution, their force increased, and recurrence facilitated, until a degree of emotional disturbance is at length excited by the merest trifles which is only worthy of some great occasion. Hence it becomes of the utmost importance for the sufferers from every form of neurosal seizure to cultivate habits of tranquillity and cheerfulness, and as regards the regulation of the emotional part of our nature, I cannot help thinking that there is much practical wisdom in the reflection I have quoted from Sterne: "I was never able to conquer any one single bad sensation in my heart so decisively, as by beating up as fast as I could for some kindly and gentle sensation to fight it upon its own ground."

Edward Liveing in *On Megrim, Sick-Headache and Some Allied Disorders,* published in 1873

Neurologic Symptoms and Signs in 347 Cases of Verified Brain Tumor

David G. Freeman, M.D., Manousos A. Petrohelos, M.D. and John W. Henderson, M.D.

In making the diagnosis of a brain tumor, the only sure method is by surgical exploration and microscopic analysis. However, in order to make a tentative diagnosis of a space taking intracranial lesion there must be a strong suspicion initiated by the patient's symptoms and confirmed by a careful neurologic examination. In analyzing the records of 347 brain tumors seen over a ten year period at the University Hospital, Ann Arbor, a purely statistical summary has been made of the symptoms and signs which occurred with sufficient frequency to be significant in the diagnosis. The purpose of this paper is to tabulate these findings according to proven anatomic location of the tumor.

The criterion of case selection was that an anatomically localizing diagnosis had been verified either by surgery, autopsy, or occasionally (as in 14 cases of pinealomas and posterior third ventricle tumors) by x-rays with contrast media only. Case selection was limited to those tumors which involved the brain directly, and not by secondary compression through the dura. The latter excluded category include tumors of the calvarium and cerebellopontine angle neoplasms such as acoustic neurinomas. Meningiomas are included in this report since they tend to invade cortical tissue by subdural extension. For the sake of clarity all percentage figures have been compiled to the nearest percentile.

IDENTIFYING DATA

Of 347 brain tumors presented, 93 (27 per cent) were infratentorial, and the remaining 254 (73 per cent) were supratentorial. The latter were divided anatomically into 18 separate categories. By far the majority were located in the frontal lobes (65 cases or 19 per cent), exclusive of parietal or temporal extension. The infratentorial tumors were placed in only two categories. These were rather arbitrarily separated anatomically with one group including those lesions occurring anterior to the fourth ventricle (midbrain, pons and medulla), and the other including fourth ventricle, cerebellar, and posterior fossa tumors.

From the departments of surgery and ophthalmology, University Hospital, Ann Arbor, Michigan.

TABLE I

IDENTIFYING DATA

Location	*Total No.*	*% of Total*	*Left*	*Right*	*Bilateral*	*Male*	*Female*	*Age*
Frontal	65	19	34	22	0	44	21	5 to 70
Frontoparietal	18	5	7	11		15	3	15 to 67
Frontotemporal	7	2	5	2		6	1	14 to 68
Temporal	29	8	18	11		20	9	9 to 60
Parietal	25	7	10	14	1	19	6	4 to 66
Temporoparietal	17	5	7	10		12	5	12 to 64
Parieto-occipital	11	3	3	8		9	2	6 to 57
Occipital	5	1	1	4		3	2	13 to 43
Diffuse (more than two lobes)	10	3				5	5	17 to 51
Corpus callosum	5	1				3	2	19 to 50
Lateral ventricles	9	3	2	6		3	6	13 to 60
Third ventricle	7	2				4	3	7 to 33
Pineal	16	5				13	3	13 to 59
Pituitary	8	2				3	5	5 to 59
Craniopharyngioma	2	1				1	1	15 to 19
Basal ganglia	5	1				2	3	10 to 21
Meningioma of sphenoidal wing	6	2	4	2		4	2	33 to 60
Optic nerve and chiasm	9	3				6	3	4 to 58
Cerebellum								
Fourth ventricle	78	23				44	34	1 to 53
Posterior fossa								
Midbrain								
Pons	15	4				11	4	9 to 60
Medulla								
TOTALS	347	100	91	90	7	227	120	1 to 70
% OF TOTALS	100	100				65	35	

In 181 cases (52 per cent) the tumor was found to be lateralized to one hemisphere. No attempt was made to lateralize the infratentorial tumors. An even division was found with 91 cases in the left hemisphere and 90 in the right. There were 227 males (65 per cent of the total) and 120 females (35 per cent). The age incidence was found to run from one year in a posterior fossa tumor to 70 years in a frontal lobe tumor. No mean age was established, but in the posterior fossa tumors there was a significantly younger age group than in the supratentorial neoplasms.

SYMPTOMS

Mental changes were found in 24 per cent of all cases. These included loss of memory, personality change, depression, confusion, and extreme lethargy. It was not surprising to find that 80 per cent of the basal ganglia, 60 per cent of the corpus callosum, and 50 per cent of the craniopharyngioma groups revealed this symptom complex. In these cases increased intracranial pressure, diffuse

TABLE 2

SYMPTOMS

Location	Mental Changes Total No.	%	Headache Total No.	%	Vomiting Total No.	%	Convulsions Total No.	%	Weakness Total No.	%	Ataxia Total No.	%	Dizziness Total No.	%	Miscellaneous Total No.	%
															(Incontinence)	
Frontal	21	32	37	57	18	28	36	53	14	22	10	15	4	6	4	6
Frontoparietal	4	22	13	72	6	33	5	28	7	39	3	17				
Frontotemporal	2	29	2	29	1	14	3	43								
Temporal	11	38	21	72	4	14	14	48							(Hypalgesia)	
Parietal	4	16	16	64	3	12	16	64	7	18	2	8			3	12
Temporoparietal	4	24	11	65	9	53	6	35	4	24						
Parieto-occipital	5	45	9	82	5	45	2	18	5	45						
Occipital			4	80	4	80					1	20				
Diffuse (more than two lobes)	3	30	7	70	5	50	4	40			2	20				
Corpus callosum	3	60	3	60			4	80			1	20				
Lateral ventricles	1	11	9	100	7	78	3	33			1	11				
Third ventricle			7	100	5	71			1	14					("Polys")	
Pineal	4	25	14	88	11	69	1	6					3	19	3	19
Pituitary	2	25	6	75	1	14									(Acromegaly)	
Craniopharyngioma	1	50	1	50							1	50			2	25
Basal ganglia	4	80	3	60	3	60	1	20	2	40						
Meningioma of sphenoidal wing	1	17	6	100	1	17	2	33							(Hypothalamic syndrome)	
Opti nerve and chiasm			7	78											1	11
Cerebellum															(Increasing head size)	
Fourth ventricle	10	13	52	67	55	71	9	13	10	13	48	62	12	15	6	8
Posterior fossa																
Midbrain																
Pons	3	20	8	53	3	20	3	20	3	20	4	27	5	33		
Medulla																
TOTALS	83		236		141		109		53		73		24			
% OF TOTALS		24		68		41		32		15		21		7		

brain involvement, and endocrine changes undoubtedly accounted for a large part of the mental impairment. It seems quite significant that 38 per cent of the temporal lobe tumors and only 32 per cent of the frontal lesions revealed changes in mentation. The neurology textbooks as a rule do not even mention mental alterations as a temporal lobe symptom, except of course for the variations of the aphasias. Some form of abnormal mental symptomatology was absent only in three tumor locations: the occipital lobe, the third ventricle, and the optic nerve and chiasm regions.

Headache was a prominent symptom and present in 236 (68 per cent) of this series of brain tumors. Three locations were found to stimulate headache in 100 per cent of cases: third ventricle, lateral ventricle, and meningioma of the sphenoidal wing. Headaches were found in over 70 per cent of the following regions: pineal, parieto-occipital, optic nerve and chiasm, occipital, pituitary, frontoparietal, and temporal lobes. It is interesting to note that the posterior fossa tumors were accompanied by headache in 67 per cent or slightly less than the average percentage of cases.

Vomiting was found in 41 per cent of the total group. As might be expected the incidence of this symptom in specific locations roughly paralleled that of headache. The exception was in the posterior fossa, where vomiting occurred in 71 per cent or almost twice that of the average incidence.

Convulsions were present in some form in 32 per cent of these brain tumors. Three locations had greater than a 50 per cent incidence, namely: 80 per cent of corpus callosum, 64 per cent of parietal, and 53 per cent of frontal lobe lesions. The temporal lobe was close behind with a 48 per cent incidence. The latter figure would probably have been higher had all the various forms of temporal lobe fits (uncinate, déjà vu, psychomotor, etc.) been recorded on the patients' charts. (Unfortunately in any tabulation such as this one is often dependent on the findings of the original examiner, and many of the recorded examinations were obviously incomplete.)

Weakness of a localizing nature was recorded on 15 per cent of the charts. Surprisingly enough 45 per cent of the parieto-occipital group revealed some degree of paresis. This was the highest percentage in any one group. Only 22 per cent of the frontal lobe lesions caused focal weakness.

An ataxic gait was a symptom in 21 per cent of the total number of tumors. This was mainly accounted for by 62 per cent of the posterior fossa group (48 cases).

Dizziness was complained of in a total of 24 or 7 per cent of patients. This was found recorded in only four categories, namely: brain stem, frontal lobe, pineal, and the largest number (12 cases representing 15 per cent) in tumors of the posterior fossa.

MENTAL SIGNS

Disorientation (and/or confusion) was found in 57 cases, or 16 per cent of the total. The greatest number of these were found in the frontal (13 cases)

TABLE 3

MENTAL SIGNS

Location	Disorientation Total No.	%	Asphasia Total No.	%	Psychic Changes Total No.	%	Intellectual Slowing Total No.	%
Frontal	13	20	5	8	13	20	24	32
Frontoparietal			4	22	1	6	7	39
Frontotemporal	3	43	2	29			4	57
Temporal	7	24	10	35			8	28
Parietal	3	12	6	24			6	24
Temporoparietal	6	35	2	12	3	18	6	35
Parieto-occipital	5	45	1	9			3	27
Occipital	1	20					1	20
Diffuse (more than two lobes)	3	30					3	30
Corpus callosum							2	40
Lateral ventricles			1	11			1	11
Third ventricle	2	28	1	14			3	43
Pineal	2	12					4 (drowsy)	25
Pituitary							3	38
Craniopharyngioma								
Basal ganglia	2	40					4 (drowsy)	80
Meningioma of sphenoidal wing	1	17	2	33	1	17		
Optic nerve & chiasm								
Cerebellum								
Fourth ventricle	6	86					11 (drowsy)	14
Posterior fossa								
Midbrain								
Pons	3	20					6 (drowsy)	40
Medulla								
TOTALS	57		34		18		96	
% OF TOTALS		16		10		5		28

and temporal (seven cases) lobes. Higher percentages (but fewer total numbers) were found in some other more diffusely situated tumors.

Aphasia was a symptom recorded in only 10 per cent of the material. The outstanding group was the temporal lobe, with ten cases (an incidence of 35 per cent).

Psychic changes (depression, euphoria, or increased emotionalism) were found almost solely in the frontal lobe localization. The latter tumors had such changes in 20 per cent or 13 cases. It is interesting to note that the temporal lobe group had a high incidence of mental deterioration but no recorded psychic changes.

Intellectual slowing was used here to denote drowsiness, lethargy, loss of memory, and even occasional cases of semi-stupor. This diminished mentation

was found in 96 cases, or 28 per cent of the total number of tumors. The frontal lobe group had the greatest number (24 cases), but the percentage incidence was quite evenly divided among all anatomic groups.

PAPILLEDEMA

The incidence of papilledema was 59 per cent, being reported for 206 of the 347 cases. Tumors which were infratentorial in location demonstrated papilledema in 70 of the 93 cases, an incidence of 75 per cent. Where the lesions could be classified as supratentorial, papilledema was present in 54 per cent (137 out of 254 cases). The process was observed to be bilateral in 199 of the 206 individuals.

TABLE 4
PAPILLEDEMA

Location	*Total No.*	*% of Total*	*Bilateral*	*Unilateral*
Frontal	30	46	29	1
Frontoparietal	9	50	7	2
Frontotemporal	3	43	3	
Temporal	15	52	15	
Parietal	13	52	13	
Temporoparietal	10	59	10	
Parieto-occipital	9	82	9	
Occipital	4	80	4	
Diffuse (more than two lobes)	7	70	7	
Corpus callosum	2	40	2	
Lateral ventricle	7	78	6	1
Third ventricle	5	71	5	
Pineal	10	63	10	
Pituitary				
Craniopharyngioma	1	10	1	
Basal ganglia	3	60	3	
Meningioma of sphenoidal wing	3	50	3	
Optic nerve and chiasm	5	56	3	2
Cerebellum				
Fourth ventricle	60	77	60	
Posterior fossa				
Midbrain				
Pons	10	67	9	1
Medulla				
TOTALS	206	59	199	7

OPTIC ATROPHY

Optic atrophy was found in 11 per cent of the cases studied. In 23 patients the changes were those of secondary atrophy; in 16 primary optic atrophy was

TABLE 5
OPTIC ATROPHY

Location	Primary Atrophy Bilateral	Primary Atrophy Unilateral	Secondary Atrophy Bilateral	Secondary Atrophy Unilateral	Total	% of Total
Frontal	2		5		7	11
Frontoparietal		2			2	11
Frontotemporal						
Temporal						
Parietal						
Temporoparietal						
Parieto-occipital						
Occipital			1		1	20
Diffuse (more than two lobes)			1		1	10
Corpus callosum						
Lateral ventricles		1	1	1	3	33
Third ventricle			1		1	14
Pineal	1		5		6	38
Pituitary						
Craniopharyngioma	3	1			4	40
Basal ganglia			1		1	20
Meningioma of sphenoidal wing						
Optic nerve and chiasm	2	2			4	44
Cerebellum						
Fourth ventricle	1		7		8	10
Posterior fossa						
Midbrain						
Pons	1				1	7
Medulla						
TOTALS	10	6	22	1	39	11

present. The greater number of cases presented atrophy in both eyes. In general, primary atrophy was associated with lesions affording direct pressure effects upon the optic nerves, while those with atrophy of a secondary type followed papilledema which resulted from obstruction of cerebrospinal fluid circulation early in the disease.

VISUAL FIELDS

A visual field examination was performed in 223 of the 347 cases. Positive findings were obtained in 73 instances, therefore the chance of demonstrating visual field changes in such cases is almost one in three. For the most part results showed either homonymous hemianopsia, bitemporal hemianopsia or peripheral constriction. The homonymous defects were mainly found in hemispheric lesions, the bitemporal changes localized almost completely to the chiasmal region, and the peripheral constrictions were of little value in placing the site of disease. Where recorded it is of interest to note the preponderance of macular sparring with the homonymous defects. The absence of quadrantanopsias in association with temporal lesions is surprising.

TABLE 6

VISUAL FIELD FINDINGS

Location	*Fields Done*	*Homonymous Hemianopsia*	*Macula Split*	*Macula Spared*	*Bitemporal Hemianopsia*	*Quadrant-anopsia*	*Peripheral Constriction*	*Central Scotoma*	*Binasal Hemian-opsia*	*Percent of Positive Findings*
Frontal	39	2		1			7	1		
Frontoparietal	14	1		1		1	1			
Frontotemporal	5						1			
Temporal	16	9		5		1	1			
Parietal	22	5					1			
Temporoparietal	9	5		2						
Parieto-occipital	8	4		2		2				
Occipital	5	3		2		1				
Diffuse (more than two lobes)	7	2	1				1	1		
Corpus callosum	5	1								
Lateral ventricles	7	1	1		1	1	4			
Third ventricle	4					1				
Pineal	10	1					2			
Pituitary										
Craniopharyngioma	8				7					
Basal ganglia	2									
Meningioma of sphenoidal wing	5						1			
Optic nerve and chiasm	8				3		1		2 (unilateral)	
Cerebellum										
Fourth ventricle	36	1	1				4			
Posterior fossa										
Midbrain										
Pons	13						2			
Medulla										
TOTALS	223	35	3	13	11	7	26	2	2	33%

CONJUGATE MOVEMENT

Defects in conjugate ocular movement were noted in the records of only 20 of the 347 cases. It is likely that some instances were overlooked in the examinations. Most of the cases were those in which the tumor location was such as to involve the pathways for ocular movement, either in the frontal lobe or the brain stem. Particular emphasis may be placed upon the upward gaze palsies found in the group of pineal tumors.

NYSTAGMUS

That nystagmus is a finding more often associated with cerebellar tumors is evident. It will also be noted that the majority of the cases demonstrating this finding were those in which the coordinative mechanism of the cerebellum,

TABLE 7

CONJUGATE MOVEMENT DEFECTS

Location	*Upward Gaze Palsy*	*Lateral Gaze Palsy*	*Miscellaneous*	*Total Cases*	*% of Total*
Frontal	2	1		3	4
Frontoparietal					
Frontotemporal					
Temporal	1		1 (weakness all directions)	2	7
Parietal					
Temporoparietal					
Parieto-occipital					
Occipital					
Diffuse (more than two lobes)	1			1	10
Corpus callosum					
Lateral ventricles					
Third ventricle					
Pineal	8	4*		8	50
Pituitary }		1		1	10
Craniopharyngioma }					
Basal ganglia					
Meningioma of sphenoidal wing		1		1	17
Optic nerve and chiasm	1			1	11
Cerebellum					
Fourth ventricle	1			1	1
Posterior fossa					
Midbrain					
Pons	1		1 (upward and downward gaze)	2	13
Medula					
TOTALS	15	7	2	20	6

*In 4 of the 8 cases listed.

TABLE 8

NYSTAGMUS

Location	*Vertical*	*Horizontal*	*Mixed Horizontal and Vertical*	*Total*	*% of Total*
Frontal		3		3	5
Frontoparietal					
Frontotemporal					
Temporal		1		1	3
Parietal					
Temporoparietal					
Parieto-occipital					
Occipital		1		1	20
Diffuse (more than two lobes)			1	1	10
Corpus callosum					
Lateral ventricles		1		1	11
Third ventricle					
Pineal	1	1		2	13
Pituitary					
Craniopharyngioma					
Basal ganglia					
Meningioma of sphenoidal wing					
Optic nerve and chiasm					
Cerebellum					
Fourth ventricle	1	14	8	23	30
Midbrain					
Pons		3		3	20
Medulla					
TOTALS	2	24	9	35	10

the brain stem, or the motor pathways was likely to be disturbed. The incidence of nystagmus was 10 per cent.

EXTRAOCULAR MOVEMENTS

Individual palsies of extraocular muscles were present in 47 cases of the group, an incidence of 14 per cent. Involvement of the abducens nerve occurred in 34 cases. The oculomotor nerve was affected in 11 instances, and the trochlear nerve was implicated in only two patients. The lack of localizing values of these findings is evident. The relatively more frequent lateral rectus palsy reflects the usual thought regarding the anatomic vulnerability of the abducens nerve.

TABLE 9

EXTRAOCULAR MUSCLE PALSIES

Location	*6th Palsy*	*3rd Palsy*	*4th Palsy*	*Total Cases*	*% of Total*
Frontal	2	1 inc.		3	5
Frontoparietal	1			1	6
Frontotemporal					
Temporal	2	1 compl.		3	10
Parietal					
Temporoparietal	2	1 inc.		3	18
Parieto-occipital					
Occipital					
Diffuse (more than two lobes)	2			2	20
Corpus callosum					
Lateral ventricles	1			1	11
Third ventricle					
Pineal	5	1 inc.		6	38
Pituitary					
Craniopharyngioma	1		1	2	20
Basal ganglia	2	1	1	4	80
Meningioma of sphenoidal wing	1			1	27
Optic nerve and chiasm	2			2	22
Cerebellum					
Fourth ventricle	10	6 inc.		16	21
Posterior fossa					
Midbrain					
Pons	3			3	20
Medulla					
TOTALS	34	11	2	47	14

OTHER CRANIAL NERVE SIGNS

The only two cranial nerve signs other than eye findings which appeared with enough regularity to be statistically significant were anosmia and facial weakness. Anosmia was reported in only 3 per cent of the total cases. Five, or 8 per cent, of the frontal lobe tumors and one, or 17 per cent, of the meningiomas of sphenoidal wing exhibited this sign.

Facial pareses were a relatively common finding, occurring in 116 cases, or 34 per cent of the total. This sign was remarkably evenly distributed among all the anatomic variants. The only exceptions were the pituitary and craniopharyngioma groups in which no cases were recorded to have facial weakness.

TABLE 10
OTHER CRANIAL NERVE SIGNS

Location	Anosmia Total No.	%	Facial Weakness Total No.	%
Frontal	5	8	25	38
Frontoparietal			6	33
Frontotemporal			4	57
Temporal	2	7	13	45
Parietal			7	18
Temporoparietal	1	6	7	41
Parieto-occipital			4	36
Occipital			1	20
Diffuse (more than two lobes)			1	10
Corpus callosum			2	40
Lateral ventricles			4	44
Third ventricle			3	43
Pineal			4	25
Pituitary				
Craniopharyngioma				
Basal ganglia			2	40
Meningioma of sphenoidal wing	1	17	3	50
Optic nerve and chiasm			3	33
Cerebellum				
Fourth ventricle			21	27
Posterior fossa				
Midbrain				
Pons			6	40
Medulla				
TOTALS	9		116	
% OF TOTALS		3		34

MOTOR SIGNS

Hemipareses, from slight weakness to hemiplegia, were found in 95 cases or 27 per cent of the total. Like facial weakness, hemiparesis was found to be remarkably evenly distributed percentage-wise among the different anatomic locations. Again the pituitary and craniopharyngioma groups exhibited no motor signs of any sort. Only six or 8 per cent, of the posterior fossa tumors were recorded to show hemiparesis. Somewhat surprising was the finding that the highest percentage (seven cases or 64 per cent was found in the parieto-occipital region.

Monoplegia of an arm was found in only 20 of the total cases (6 per cent). Paresis of a leg was found in half that number. Both these findings occurred in scattered locations.

TABLE 11
MOTOR SIGNS

	Hemiparesis Total		——Monoparesis—— Arm Total		Leg Total		Ataxia of One or More Extremity Total		Ataxic Gait Total	
Location	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Frontal	22	34	2	3	3	5	10	15	8	12
Frontoparietal	6	33	4	22	1	6	2	11	1	6
Frontotemporal	2	35	2	29	1	14			1	14
Temporal	12	41	2	7	2	7	6	21	1	4
Parietal	12	48	4	16			1	4	2	8
Temporoparietal	7	41	2	12	1	6	3	18	4	24
Parieto-occipital	7	64			1	9	1	9	1	9
Occipital							2	40		
Diffuse (more than two lobes)	3	30					3	30	2	20
Corpus callosum	2	40					1	20		
Lateral ventricles	2	22					3	33	3	33
Third ventricle							2	18	3	43
Pineal	3	19					3	19	4	25
Pituitary										
Craniopharyngioma									1	50
Basal ganglia	1	20					1	20		
Meningioma of sphenoidal wing	2	33	1	17	1	17	1	17		
Optic nerve and chiasm										
Cerebellum										
Fourth ventricle	6	8	3	4			40	51	53	68
Posterior fossa										
Midbrain										
Pons	7	47					5	33	6	40
Medulla										
TOTALS	95		20		10		84		90	
% OF TOTALS		27		6		3		24		26

Ataxia of gait was present in 90 cases (26 per cent of total). By far the major portion of these were found in the posterior fossa tumors (53 cases or 68 per cent of the latter). Lack of coordination, or ataxia, of one or more extremities was found in 84 cases, or 24 per cent of the total. This sign was found in 51 per cent (40 cases) of posterior fossa lesions.

SENSATION

A diminution in some form of cutaneous sensation (36 cases, or 10 per cent of the total) and astereognosis (19 cases, or 5 per cent of the total) were the only sensory findings recorded with sufficiency to be significant in this series.

TABLE 12

SENSATION

Location	Diminished Cutaneous Sensation Total No.	%	Astereognosis Total No.	%
Frontal	9	14	5	8
Frontoparietal	2	11		
Frontotemporal	1	14	1	14
Temporal	4	14	1	4
Parietal	5	20	5	20
Temporoparietal	4	24	4	24
Parieto-occipital	4	36	1	9
Occipital	1	20		
Diffuse (more than two lobes)	2	20		
Corpus callosum	1	20		
Lateral ventricles			1	11
Third ventricle				
Pineal	1	6	1	6
Pituitary				
Craniopharyngioma				
Basal ganglia				
Meningioma of sphenoidal wing				
Optic nerve and chiasm				
Cerebellum				
Fourth ventricle				
Posterior fossa				
Midbrain				
Pons	2	13		
Medulla				
TOTALS	36		19	
% OF TOTALS		10		5

Those cases in which the parietal lobe was involved by tumor had by far the highest incidence of sensory findings. These signs were present in 25 cases, or 35 per cent of tumors which were located in or invaded the parietal lobes.

REFLEXES

Hyperactive tendon reflexes of one or more extremity were found in a total of 116 cases or 34 per cent. This finding did not appear to be predominantly in either arm or leg in any of the anatomic groups. Surprisingly enough the parieto-occipital group had as large a percentage of hyper-reflexic cases as the frontal lobe tumors, both having 55 per cent incidence. The fronto-parietal group had the largest percentage of any anatomic location, 61 per cent of these being hyper-reflexic.

TABLE 13

REFLEXES

	Hyperactive Tendon Reflexes						Hypoactive Tendon Reflexes		Babinski							
	Arm		Leg		No. Patients				Unilateral		Bilateral		Stiff Neck		Clonus	
	Total		Total		Total		Total		Total		Total		Total		Total	
Location	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Frontal	31	48	25	38	36	55	3	5	25	38	6	9	1	2	5	8
Frontoparietal	9	50	9	50	11	61	1	6	6	33	3	17			3	17
Frontotemporal	2	29	2	29	2	29			3	43	1	14				
Temporal	11	38	10	35	11	38			7	24	1	4	2	8	1	4
Parietal	10	40	7	18	10	40	1	4	6	24	1	4			1	4
Temporoparietal	4	24	4	24	5	29			5	29	2	12			1	6
Parieto-occipital	6	55	5	45	6	55	1	9	6	55						
Occipital	1	20	1	20	1	20	1	20	1	20						
Diffuse (more than two lobes)	1	10	2	20	2	20	2	20	5	50						
Corpus callosum			1	20	1	20			1	20						
Lateral ventricles	2	22	1	11	2	22			2	22	1	11	1	11		
Third ventricle	1	14			1	14			2	28			1	14		
Pineal	2	12	2	12	2	12			5	31	1	6	2	12		
Pituitary																
Craniopharyngioma			1	50	1	50										
Basal ganglia	2	40	2	40	2	40			2	40					1	20
Meningioma of sphenoidal wing	2	33			2	33	1	17	1	17						
Optic nerve & chiasm	1	11	3	33	3	33	2	22	3	33						
Cerebellum																
Fourth ventricle					16	21	16	21	20	26	11	14	9	13	3	4
Posterior fossa																
Midbrain																
Pons	1	7	2	13	2	13	2	13	2	13	1	7	2	13	2	13
Medulla																
TOTALS					116		30		102		28		18		17	
% OF TOTALS						34		9		30		8		5		5

TABLE 14
SUMMARY

	Total Number of Patients	Percent of Total
INDENTIFYING DATA:		
Total number	347	100
Left hemisphere	91	52
Right hemisphere	90	
Male	227	65
Female	120	35
SYMPTOMS:		
Mental change	83	24
Headache	236	68
Vomiting	141	41
Convulsions	109	32
Weakness	53	15
Ataxia	73	21
Dizziness	24	7
MENTAL SIGNS:		
Disorientation	57	16
Aphasia	34	10
Psychic change	18	5
Intellectual slowing	96	28
CRANIAL NERVE SIGNS:		
Anosmia	9	3
Papilledema	206	59
Optic atrophy	39	11
Visual field findings	73	33*
Conjugate movement defects	20	6
Nystagmus	35	10
Extraocular muscle palsies	47	14
Facial weakness	116	34
MOTOR SIGNS:		
Hemiparesis	95	27
Monoparesis		
Arm	20	6
Leg	10	3
Ataxia of extremities	84	24
Ataxic gait	90	26
SENSATION:		
Diminished cutaneous sensation	36	10
Astereognosis	19	5
REFLEXES:		
Hyperactive tendon reflexes	116	34
Hypoactive tendon reflexes	30	9
Babinski	102	30
Babinski (bilateral)	28	8
Stiff neck	18	5
Clonus	17	5

*Percentage of positive findings in total number of cases having visual field examinations.

Hypoactive reflexes were found to be very unreliable localizing signs. These were recorded in 30 cases, or 9 per cent of the total. Sixteen cases (21 per cent) of posterior fossa tumors were found to have hyporeflexia. In other groups in which this finding was recorded one becomes suspicious of hyporeflexia as only reflecting the hyper-reflexia of the contralateral side.

An extensor plantar response (Babinski) was noted in 102, or 30 per cent of total cases, and a bilateral Babinski in 28 cases, or 8 per cent. The unilateral response was remarkably evenly distributed throughout all the anatomic groupings.

Stiff neck was a finding in 13 per cent of both posterior fossa (nine cases) and the midbrain, pons, and medulla (two cases) groups. The percentage of cases in the above mentioned groups was directly proportional to the meticulous care with which the neurologic examination had been recorded. This sign is thought to be far more significant than might be expected from the 11 positive findings recorded.

SUMMARY

Three hundred forty seven cases of proved brain tumors are reported in terms of their anatomic location and the significant neurologic symptoms and signs produced.

Clinical Significance of the Dissociation of Abdominal Reflexes

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We have made the object of our examination the behavior of the superficial and deep abdominal reflexes, that is, the abdominal skin reflex (*asr*) and the abdominal muscle reflex (*amr*) in various neurologic diseases. Modern neurologic textbooks and other literature either do not indicate at all the differences between these two types of reflexes, or else classify them under such names as diaphragmatic, costoabdominalis, symphysis reflexes, and so forth. The resultant difficulty in evaluation is the reason this investigation was undertaken.

The first comprehensive survey was made by Wartenberg.[1] According to him the abdominal muscle reflex is a stretch reflex. Its reflexogenous zone is, corresponding with its points of insertion, a very extensive one: the costal margin, the pelvis, and the muscle itself. For its elicitation Wartenberg recommends two methods: 1.) pressing a ruler upon the abdominal wall, lateral to the umbilicus, and tapping it; 2.) tapping one's own finger, laid on the symphysis. Other methods of elicitation (figure 1): tapping of the nipple (Hess, 1906); the symphysis (Guillain-Alajouanine, 1927, Benedek-Angyal, 1942); the abdominal muscle (Trömner, 1926, Robinovitch, 1935); the spina iliaca anterior superior (Gallant, 1926); the costal border inside the mammillary line (Bechterew, Purves-Stewart, Monrad-Krohn, 1927); the tuberculum pubis, or the Poupart ligament (Astwazaturow-Triumphoff, 1927); the anterior and outer parts of the thoracic wall (Weingrow, 1936); or stretching the abdominal muscle in all the four quadrants by inserting a finger in the umbilicus and tapping it (Nielsen, 1941) .

It is essential in all these methods of elicitation to bring about a contraction of the abdominal muscle. The quoted authors gave the reflex different names according to the point of elicitation, and consequently there arose the well known reflex names, such as mediopubicus, costoabdominalis, symphysis, pyramidal, and so on.

METHOD

The abdominal muscle was tapped directly, either by pressing the stiffened index finger upon the abdominal wall, or, following Nielsen's method, by in-

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TABLE 1

ABDOMINAL SKIN AND MUSCLE REFLEX DISSOCIATION IN 500 CASES

	Number of Cases	%
Myelopathy	15	86.6
Multiple sclerosis	200	77
Syringomyelia	4	75
Spinal cord tumor	15	53.3
Hemiplegia	45	28.8
Tabes dorsalis	26	11.5
Central nervous system syphilis	75	9.2
Parkinsonism	20	5
Neurasthenia	100	2

serting the left index into the umbilicus, so stretching the abdominal muscle, and then tapping the finger briskly with a percussion hammer. The Guillain-Alajouanine muscle reflex was controlled in each case. The skin reflex was elicited by the use of Wartenberg's pinwheel.

CASE MATERIAL

Our material included 500 cases, classified according to disease as shown in table 1; 100 neurasthenic patients were used for control purposes. In the central nervous system group, those patients with syphilis and focal symptoms were excluded. Hemiplegia was examined as a syndrome; it was generally caused by softening or bleeding from cerebral arteriosclerosis. The great majority of cases of parkinsonism were postencephalitic, the minor part arteriosclerotic. In the myelopathy group were included cases with spinal cord degeneration.

Examinations were performed on adult patients. This is mentioned because the abdominal reflex develops between the third month and the fourteenth year, at the same time when the plantar reflex appears.[2]

We have found among the examined diseases seven with "complete" abdominal reflex dissociation (table 1). By this is to be understood that the abdominal skin reflex was completely absent; on the other hand the abdominal muscle reflex was elicitable or exaggerated. The dissociation was in evidence in decreasing succession as follows: myelopathy, 86.6 per cent; multiple sclerosis, 77 per cent; syringomyelia, 75 per cent; spinal cord tumor, 53.3 per cent; tables, 11.5 per cent; central nervous system syphilis, 9.2 per cent; parkinsonism (one single case), 5 per cent; neurasthenia (partial dissociation in two cases), 2 per cent. It remains an unanswered question whether these cases could be considered as candidates for organic diseases, or whether they are to be ascribed to the imperfection of the examination. The number of the syringomyelia cases was too small to draw a conclusion from the high percentage of dissociation.

Thus there are seven diseases in which dissociation was found, and three in which it could have some diagnostic significance on the basis of the high

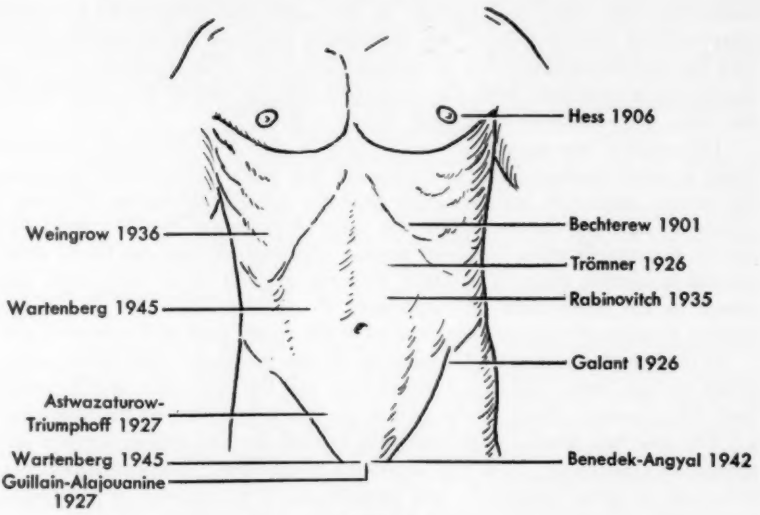

FIGURE 1.

percentage of incidence: myelopathy, multiple sclerosis, and spinal cord tumor. It is noteworthy that these are three diseases in which the differential diagnosis may be problematical.

The percentage figures for myelopathy and multiple sclerosis are similar. The fact that these two clinically and anatomically similar diseases behave identically with regard to the abdominal reflexes indicates the possibility that reflex dissociation appears mainly in disseminated lesions of the spinal cord.

Twenty-six cases of tabes dorsalis were the object of special studies. In nine cases both abdominal reflexes were absent; in four cases they were all positive; in eight dissociation could be observed. In five cases the *asr* was positive and the *amr* negative; in three cases just the reverse was noted. The former cases are explicable in tabes where the deep muscle reflexes are absent, but the dissociation can only be explained by the assumption that in these segments of the dorsal spinal cord the fibers of superficial, and not those of deep sensation were, by some reason, involved by the process. Besides that, the frequency of these cases is so negligible (11.5 per cent) that no importance can be attributed to them in differential diagnosis.

DISCUSSION

The different behavior of the abdominal muscle and skin reflexes, that is to say, the dissociation of the abdominal reflex, was first mentioned by Guillain Alajouanine and Marquezy in 1924.[3] In half of 22 multiple sclerosis cases the mediopubical reflex, described by them, was elicitable, while the

abdominal skin reflex was absent. In the same year Monrad-Krohn stated also, without statistical data, the dissociation between the costoabdominalis and the abdominal skin reflex in multiple sclerosis.[4] The significance of both statements is identical: both the symphysis reflex as well as the costoabdominal reflex are essentially abdominal muscle reflexes.

Dissociation was mentioned by Nippert in that the abdominal periosteal reflex is more constant than the abdominal skin reflex. After brain operations the former returns to normal earlier than the latter. Olivecrona observed a difference between the two reflexes in cases of pritonitis: the skin reflex was absent, the muscle reflex remained normal. Triumphoff[5] has also found dissociation in certain cases of multiple sclerosis as well as in hemiplegia and tabes; on the other hand he emphasizes the identical behavior of the two reflexes in cases of poliomyelitis, lesions of the spinal cord and syringomyelia.

Rabinovitch[6] has tested the behavior of the percussive abdominal reflex, called by him "reflex abdominal percutoire," and the skin reflex in 118 normal and 314 pathologic cases. In the pathologic group he observed the following: 1.) The *amr* was normal in polyneuritis, central nervous system syphilis and pyramidal syndromes; 2.) it was increased in epilepsy, encephalopathy, certain cases of tabes, radiculitis, and myelitis; 3.) it was absent in paraplegia, hemiplegia, syringomyelia, spinal compression and multiple sclerosis.

Foerster[7] discriminates between abdominal skin and deep reflexes. In hemiplegia, *asr* and cremaster reflex were absent on the side of the lesion and the deep reflexes were exaggerated. This dissociation is, in his opinion, constantly present in cases of multiple sclerosis. It occurs as well in spinal cord tumors, spondylitis, traumatic lesions of the spinal cord, myelosis, and so on. Dissociation is considered by Foerster to be one of the most sensitive signs of a lesion in the supranuclear region.

In 1937 Kastein[8] treated the reflex dissociation in cases of lesions of the pyramidal tract; in 1941 Nielsen dealt with the problem.

Teschler[9] mentioned in 1943 the deviation between the costoabdominal reflex and the abdominal skin reflex which, in his opinion, might be used as a sign in oligosymptomatic cases of multiple sclerosis.

In 1946 Wartenberg[1] emphasized the fact that the absence of muscle reflex alone has no great clinical significance. It becomes important: 1.) if the skin reflex is absent at the same time, for this shows the lesion of the corresponding segment below T6; 2.) if the muscle reflex is exaggerated on both sides and *asr* is absent at the same time; this is an authentic sign of a pyramidal lesion of the segment above T6. He considers the exaggeration of the abdominal muscle reflex as an earlier, better and more reliable sign of pyramidal lesion than the absence of the abdominal skin reflex.

In connection with the abdominal skin reflex Wartenberg calls our attention to the following facts: 1.) It can be present also in pronounced pyramidal lesions. 2.) The abdominal skin reflex may recover before the recovery of the spinal cord lesion. 3.) The diminishing of the reflex is in no proportion to the

degree of the pyramidal lesion. 4.) In multiple sclerosis it may be absent in a very early stage, when no other pyramidal signs are yet present.

Monrad-Krohn[10] registered a difference between deep muscle reflex, cutaneaces, abdominal reflex, and pathologic abdominal reflex. The latter is, in his opinion, just as pathologic a compensatory reflex (Ersatzreflex) as the Babinski sign in the lesion of the pyramidal region.

The characteristics of pathologic abdominal reflexes are, in his opinion, as follows: 1.) Their latent time is longer than that of normal abdominal reflexes. 2.) They have a bilateral and reacting character. 3.) They are elicitable by warm and cold stimulation and by pinching the skin. 4.) They are accompanied by other reflex actions. The significance of the pathologic abdominal reflex is that by this the lowest point of the spinal lesion can be decided.

We examined the first two types: the deep muscle, and the superficial skin reflexes. The clinical and pathologic abdominal reflex does not seem to be sufficiently clarified. It may be a pathologic exaggeration of the deep muscle reflex, thus it can be considered as an equivalent of the Babinski sign, as e. g. the pathologic exaggeration of the normal plantar reflex. This opinion is supported by Monrad-Krohn's observation that this reflex is bilateral, which means that the exaggeration of the reflex is accompanied by irradiation.

CONCLUSIONS

1. The examination of the abdominal muscle reflex is one of the important procedures of organic neurology. It should be carried out as well as observation of the abdominal skin reflex. In certain diseases *asr* is absent, at the same time *amr* is elicitable or even exaggerated. This is called abdominal reflex dissociation, which can be total or partial. Importance can be attributed to the complete dissociation only.

2. Dissociation means that *amr* follows the behavior of the other deep reflexes (patellar, Achilles, and so on); *asr* that of the superficial reflexes.

3. The dissociation of the abdominal and skin reflexes has no pathognomic meaning. From the examined diseases it appears most frequently in myelopathy and multiple sclerosis, 86.6 per cent and 77 per cent respectively; in spinal cord tumors, 53.3 per cent; in hemiplegia, 28 per cent; in tabes, 11 per cent; in central nervous system syphilis, 9.2 per cent. The high percentage in syringomyelia cannot be evaluated on account of the small number of cases.

The observed changes in parkinsonism and neurasthenia were partial reactions only, so they may be neglected from the point of view of our problem.

The abdominal reflex dissociation can be very well used as a support of the diagnosis. Thus the frequency of intention tremor in multiple sclerosis is 43 per cent; that of nystagmus, 68 per cent; of optic system changes, 78 per cent.[11] In relation to these, the 77 per cent of the abdominal dissociation seems to be a valuable datum.

It is difficult to give an explanation of the deviation of *asr* as its path is unknown. We have no other resources but only assumptions, since there is

no abdominal skin reflex among animals. Aronovitch[12] could elicit only one of the abdominal muscle reflexes in apes. According to Monrad-Krohn's newest statements,[10] Fulton succeeded in finding abdominal reflexes in chimpanees, which often disappeared at the removal of the premotor area.

A complete absence of abdominal reflexes in arteriosclerosis was found by Monrad-Krohn in 56 per cent of the cases; among 15 paralysis agitans patients the abdominal reflex was absent in two cases. He considers the one-sided absence in the diagnosis of brain tumors very important; this may often appear as the first symptom without any other reflex deviation or spasticity. In this case Monrad-Krohn supposes a lesion of the parietal area, and Janowitz that of the frontal area.

All the investigators agree with the theory that the abdominal skin reflex is not a common spinal reflex, but its reflex arc probably reaches the brain, thus it is a cerebral reflex. The only exception is Delmar-Marsalet, in whose opinion the spinal origin cannot be doubted. His opinion is not supported.

It was Monrad-Krohn who deal thoroughly with the assumed path of *asr*. He thought it probable that the afferent tract is the posterior funiculus, although possibly also in the lateral funiculus; the efference path is in the pyramidal tract. The latter theory has been generally accepted.

The subject was of deep interest to Foerster[7] who tried in operations to clarify the descent of the afferent path by cutting the different tracts of the spinal cord. He stated that by cutting the posterior the funiculus *asr* remained preserved, by cutting the anterior or lateral column, the *asr* sometimes disappeared or decreased, but there was no constant absence.

We attribute great importance to Foerster's statement that by eradicating the cortical motor root and trunk centers the opposite *asr* was absent for several months, and remained constantly weaker than the normal side.

This observation is, in our opinion, suitable to prove the cortical origin of the *asr*. This seems to be ascertained by Fulton's animal experiments.

As conclusions to the above, the path of the reflex arc is as follows: The stimulus passes from the skin of the abdominal wall to the spinal cord, probably to the crossed spinal-thalamic tract. From the thalamus it passes either (1) to the Brodmann fields, 1, 2, 3 and from thence to one 4, spreading to the prefrontal area and thence descending through the pyramidal tract in the spinal cord; or (2) from the nuclei of the thalamus to the striatum, the red nucleus and through the rubrospinal tract in the spinal cord. Of these two hypothetical suppositions the former is supported by Foerster's surgical experiments and by clinical experience.

In contrast to the path of the abdominal skin reflex, the abdominal muscle reflex is a spinal cord reflex similar to the patellar and the Achilles reflexes. Thus the absence of *asr* indicates a lesion of the afferent sensory, the efferent motor nerve, or of the corresponding segment of the spinal cord. The exaggeration of *amr* is just as much a sign of a pyramidal lesion as the exaggeration of the other deep muscle reflexes.

4. We agree with Wartenberg when he demands a simplification of the complicated reflexology. On the other hand, the reflexes lose their value in clinical diagnostics by excessive simplification.

Reflexes are clinical conceptions, thus the circumstances of the clinical elicitation cannot be neglected, because these will give the individuality and the semiological value of the reflex.[14]

SUMMARY

1. The behavior of abdominal skin and abdominal muscle reflexes was examined in 500 cases. In seven diseases a "complete" abdominal reflex dissociation was found: in myelopathy, 86.6 per cent; multiple sclerosis, 77 per cent; syringomyelia, 75 per cent; spinal cord tumor, 53.3 per cent; hemiplegia, 28.8 per cent; tabes, 11.5 per cent; central nervous system syphilis, 9.2 per cent. In parkinsonism (5 per cent) and neurasthenia (2 per cent) a partial dissociation was observed, the value of which is questionable. The syringomyelia cases were too few to draw conclusions.

2. Dissociation is most frequent in those three diseases, the clinical differentiation of which is especially difficult (multiple sclerosis, myelopathy, spinal cord tumor).

3. "Complete" abdominal reflex dissociation occurs most frequently in diseases of the spinal cord with disseminated foci. It has no absolute diagnostic value, but it can be utilized in the clinical symptomatology.

4. The examination of *amr* and thus the search of the dissociation of *asr* and *amr* is a valuable and important datum of organic neurology.

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Radioisotope Investigations on the Blood-Brain and Blood-Liquor Barrier

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THREE types of experiments have been carried out: 1) isotope encephalometry following angiography; 2) attempts to detect changes in the blood-liquor barrier resulting from changes in intracranial pressure; 3) quantitative evaluation of the relative amount of I^{131} in blood and cerebrospinal fluid in various diseases.

ISOTOPE ENCEPHALOMETRY FOLLOWING ANGIOGRAPHY

Contralateral hemiparesis or other less severe neurologic symptoms appear with sufficient frequency following carotid angiography to render the procedure somewhat hazardous. With the use of radioactive iodinated serum albumin for isotope encephalometry,[1,2] a relatively high isotope blood level is maintained for several days. This made it possible to count patients after angiography, and in some cases both pre- and postangiography, to see if there were a substantial change in the count of the injected hemisphere following the procedure. An increased count would indicate increased permeability of the blood-brain barrier, increased blood flow, or increased blood volume, or some combination of these factors. A decrease in the count would indicate a possible reverse of these changes.

This work was originally stimulated by the discovery of a definite increase in the count of the injected hemisphere following an angiogram in a patient who developed a hemiparesis shortly thereafter. The increased uptake of this hemisphere decreased as the hemiparesis improved.

Method

A modification of the routine method of counting patients suspected of having a brain tumor was used. A rubber bathing cap, marked symmetrically with the different detector positions, was used during all counting to insure exact duplication of counting positions in the pre- and postangiogram counts.

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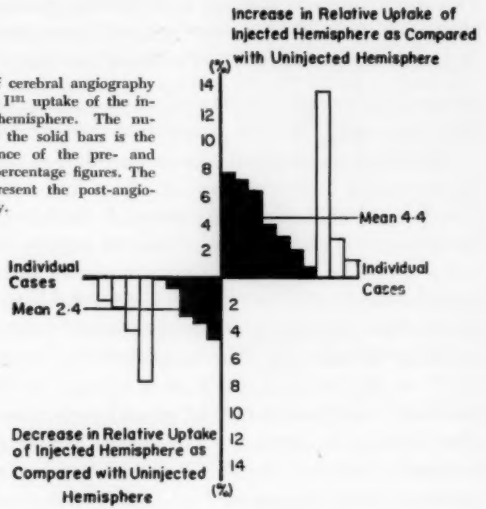

FIG. 1. Effect of cerebral angiography upon radioactive I^{131} uptake of the injected cerebral hemisphere. The numerical value of the solid bars is the algebraic difference of the pre- and post-angiogram percentage figures. The hollow bars represent the post-angiogram counts only.

The scintillation counter used for brain tumor detection work[3] was used in all cases. Counts in the routine positions were done in most cases, and the total count of each hemisphere was computed. The smaller sum was then subtracted from the larger and the difference divided by the larger to obtain the percentage difference. It was determined, in a series of counts upon 20 patients who had not had angiography and who had no isotope focus, that the average range of variation of the total count of one hemisphere from the other was 2 per cent.

The results are graphed in figure 1.

Analysis of results: There were ten cases which showed a homolateral increase in radioactive I^{131} uptake following angiography, and ten cases which showed a decrease. Seven of the former and five of the latter had pre- and postangiogram counts, and only these were used for analysis. The mean increase was 4.4 per cent; the mean decrease 2.4 per cent. The material was also analyzed according to the length of time the iodinated albumin had been in the body prior to the time of counting and according to the time proximity of the pre- and postangiogram counting to the angiogram. These variables have not significantly influenced the results in this series of experiments.

Conclusion: It seems apparent that, following a carotid angiogram with 35 per cent Diodrast, the injected hemisphere as compared with the opposite hemisphere shows an increase in counts more often than a decrease, and that this mean increase is greater than the mean of those who have a decrease.

This study seems to indicate that vascular permeability change, or change in blood volume or flow in the injected hemisphere following angiography, is slight and insignificant except in those rare cases when hemiplegia follows.

ATTEMPTS TO DETECT CHANGES IN THE BLOOD-LIQUOR BARRIER RESULTING FROM CHANGES IN INTRACRANIAL PRESSURE

This problem has great clinical importance, particularly in relation to brain edema and to hydrocephalus. Relative concentration of I^{131} has been determined in blood and in cerebrospinal fluid by a method described below. However, because of the small size of animal ventricles (even after production of hydrocephalus),[4] and many variables and artifacts that cannot be adequately controlled, it has not yet been possible to demonstrate valid and exact quantitative relationships between barrier damage and pressure change. It can only be said that there appears to be marked increase in concentration of I^{131} in the cerebrospinal fluid in relation to simultaneous blood level after increase in cerebrospinal fluid pressure, and also a somewhat similar change after decrease in pressure. This change following decrease in pressure could be readily explained by the increased pressure gradient, but that following increased pressure must be explained by a humoral or neurogenic mechanism resulting from the increased pressure. Refinements of technique are now being attempted.

Several experimental observations have been made on humans: 1.) Increase in radioactive I^{131} concentration per unit volume of spinal fluid was found after pneumoencephalogram with room air. 2.) A hydrocephalic baby, in whom the ventricles were allowed to drain freely to the external surface of the head, showed a progressive lowering of the relative concentration of I^{131} in the cerebrospinal fluid as compared with blood during a two day drainage period. 3.) A patient with a chronic cerebrospinal fluid fistula into the nose, showed in the excreted fluid an I^{131} uptake which was tremendously increased over that expected in the cerebrospinal fluid of a normal person. There is recent evidence, however, to indicate that paranasal glands may concentrate I^{131}.[5]

QUANTITATIVE EVALUATION OF RELATIVE AMOUNTS OF I^{131} IN BLOOD AND CEREBROSPINAL FLUID

Previous experimentation indicated that rarely was any detectable gamma radioactivity present in the cerebrospinal fluid of patients who had received I^{131} as diiodofluorescein. It was therefore felt desirable to develop an accurate method of beta as well as gamma counting, hoping thus to detect much smaller amounts of I^{131}.

Development of a counting method:

A large amount of experimentation was necessary to develop a satisfactory method of performing beta and gamma counting upon small samples of

blood and cerebrospinal fluid with a minimum of possible error.*

Cerebrospinal fluid and blood samples are obtained at the same time and the ratio of blood activity to that of the cerebrospinal fluid is calculated. I^{131} albumin was the isotope used in these experiments. If blood is present in the spinal fluid, which was very rare, a correction factor can be calculated, knowing the relative number of red blood cells present in spinal fluid and peripheral blood, and assuming that the number of red cells in the spinal fluid is approximately in direct proportion to the amount of whole blood which entered the spinal fluid as the result of needle puncture. Also it has been found that in the case of I^{131}, scatter and self absorption do not introduce significant errors.[7] Total error of these experiments was calculated at the begining of the study as S.D. $\pm$ 6.6 per cent. In some determinations, when spinal fluid activity was low, it became larger. At the present time, with more careful control of technique and counting time, the error seldom exceeds a total spread of $\pm$ 2 per cent.

Results: Eighteen cases are analyzed in figure 2. The length of the bars is inversely proportional to the relative concentration of I^{131} in the spinal fluid. It is apparent that the tumor group tend to have higher I^{131} concentration than the chronic degenerative diseases. The I^{131} concentration was plotted against dosage of I^{131}, the amount of previous iodine given to block the thyroid, the length of time the I^{131} had been in the body at the time of counting, and the blood level of I^{131} at the time of lumbar puncture. No significant cor-

*The method of preparation of counting samples has been modified from a method developed by the department of physiological chemistry of the University of Minnesota.[7] The following method is used: .04 cc. of glycerol is pipetted upon a copper planchette 25 mm. in diameter. To this a few flecks of a solid detergent (Nacconol, a laboratory cleansing agent, manufactured by National Aniline Division, Allied Chemical and Dye Corporation, Merchandise Mart, Chicago) is added and a 0.5 cc. sample of cerebrospinal fluid. The total sample is then distributed evenly over the entire planchette, if necessary, by blowing upon it through a capillary tube, or by an extremely fine wire, curved at its tip. Blood samples are prepared in a similar manner except that the blood is first hemolyzed by adding an exactly equal volume of distilled water and the proper amount of glycerine and "Nacconol" is added to the blood in the test tube. Whole blood samples will crack and fragment. It is necessary to use heparinized blood in order to avoid the loss of radioactivity incident to the use of oxalate.[6] Potassium iodide carrier may be added in equal volumes to blood and spinal fluid. However, the results of the same samples when carrier was used and when it was not have been compared in many cases, and a difference which exceeded one standard deviation of error has never been found. Dilution of a weak sample with carrier necessitates a very long counting period. As a dessicator the following apparatus is used, routine dessicators being found to be unsatisfactory; a 10 inch square of plate glass is rendered exactly level at a convenient height for pipetting. The planchettes are placed in a circle on this plate and locations numbered. The samples are then pipetted onto the planchettes. A Petri dish containing P_2O_5 is placed in the center of the ring of planchettes and the whole is covered by an 8 inch watch glass with edges ground to fit the plate glass. The joint is sealed with stop-cock grease. Drying is adequate in 24 to 48 hours. The planchettes are then counted as close as possible to the window of a mica window Geiger-Muller tube. The use of a gas flow counting chamber will increase the counting rate in the ratio of 1.7 to 1.0, and would probably increase it more if a softer beta emitter were used. The geometrical conditions of counting must, of course, be exactly the same at each counting.

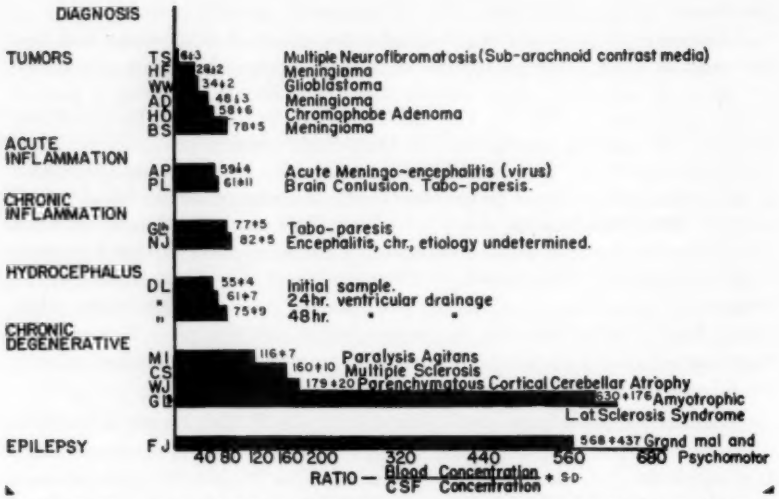
DIAGNOSIS
TUMORS
TS 4±3 Multiple Neurofibromatosis (Sub-arachnoid contrast media)
HF 28±2 Meningioma
WW 34±2 Glioblastoma
AD 46±3 Meningioma
HO 58±6 Chromophobe Adenoma
BS 78±5 Meningioma
ACUTE INFLAMMATION
AP 59±4 Acute Meningo-encephalitis (virus)
PL 61±11 Brain Contusion. Tabo-paresis.
CHRONIC INFLAMMATION
GL 77±5 Tabo-paresis
NJ 82±5 Encephalitis, chr., etiology undetermined.
HYDROCEPHALUS
DL 55±4 Initial sample.
61±7 24hr. ventricular drainage
75±9 48hr. " "
CHRONIC DEGENERATIVE
MI 116±7 Paralysis Agitans
CS 160±10 Multiple Sclerosis
WJ 179±20 Parenchymatous Cortical Cerebellar Atrophy
GL 530±176 Amyotrophic Lat Sclerosis Syndrome
EPILEPSY
FJ 568±437 Grand mal and 680 Psychomotor
40 80 120 160 200 320 440 560
RATIO — Blood Concentration / CSF Concentration ± SD

FIG. 2. Concentration of I^{131} in cerebrospinal fluid in relation to simultaneous blood concentration. $\frac{(\text{Blood Conc.})}{(\text{C.S.F. Conc.})}$ Note the difference between tumors and chronic degenerative diseases.

relation was found in any of these comparisons except that the cases with low activity in the spinal fluid have tended to have short intervals between injection of I^{131} and lumbar puncture, and to have higher blood levels of I^{131} at the time of lumbar puncture.

It is possible that the test may have some diagnostic value, particularly between tumors and chronic degenerative diseases.

SUMMARY

Three groups of experiments, which demonstrate the usefulness of the isotope method in neurologic investigations upon humans, are presented.

1. Isotope encephalometry in close proximity to cerebral angiography has failed to demonstrate any marked change in uptake of radioactivity of the injected hemisphere, except when profound neurologic deficit resulted from the angiogram.

2. Changes in intracranial pressure appear to alter the blood-liquor barrier, but exact quantitative relationships have not been established.

3. A method has been developed to perform beta and gamma counting accurately upon comparative samples of blood and cerebrospinal fluid. Marked differences have been found between the ratios in tumors and in chronic degenerative diseases, but the value of the test is still to be proved.

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A certain degree of nausea is a tolerably constant feature of megrim. In some cases it is slight, in others it reaches a high degree of intensity, and is followed by vomiting.

Out of the 60 cases I have analysed, 23 stated that their attacks were generally or always attended with vomiting or violent retching; 9 complained only of occasional vomiting; 16 suffered for the most part from nausea alone, but of these 7 stated that they also occasionally vomited.

M. Piorry and Dr. Dwight have described in nearly the same terms the sense of disgust for food with which the attack sometimes begins, and the latter traces its further development into nausea and vomiting. "From the beginning there is a total loss of appetite; an aversion to every flavor, even to those which are at other times the most grateful. . . . From an aversion to food the stomach feels an uneasiness which is indescribable, but speedily rises to a greater or less degree of nausea. In some instances it soon becomes sufficiently strenuous to excite a voluntary retching to vomit. . . . In other instances the nausea becomes very distressing, but does not produce a retching. In these cases the disease generally continues much longer, and is perhaps none the less painful."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by J. M. Nielsen, M.D.

CASE PRESENTATION

A 55 year old married woman was seen in a hospital September 20, 1951, as a brain tumor suspect because of episodes of mental disturbance with loss of consciousness. After air encephalogram and electroencephalogram she was considered a medical problem and was referred for management.

The history obtained from relatives showed that her husband had died a year before of a "stroke." She had one married daughter and a married son. They did not know her recent history. The patient spoke with some dysarthria and her ideation was not clear; yet she denied nervous breakdown, heart trouble, diabetes, tuberculosis, and kidney trouble but admitted high blood pressure. She denied operations and accidents. Only an occasional cocktail was admitted; otherwise she did not drink.

The patient was unable to give an orderly account of her illness. She even said she had no home address and she did not know the month. She said, "I sprained my ankle and a few things happened. I guess I was unconscious and taken to the hospital in Salt Lake in August. I doctored at the Holy Cross Hospital in Salt Lake." She said she had come directly to Los Angeles. When asked about her voice (dysarthria) she said, "Well, Dr. Raney taught me to talk. I hadn't talked for three days." She told of her two children in Los Angeles.

Physical examination showed a well nourished woman of 55 years with evidence of childhood rickets and with a flabby musculature. Temperature was 98.4° F., blood pressure 140/80, pulse rate 75, and respirations 16 per minute. The heart was slightly enlarged to the left but the tones were clear and the lungs were normal. The brachial arteries were sclerosed. The thyroid gland was not palpable and the abdomen was negative.

The urinalysis showed a specific gravity of 1.022, a trace of albumin but neither sugar nor acetone. A blood count showed a hemoglobin content of 85 per cent, 4.45 million red and 12,500 white cells per cu. mm., with 60 per cent polymorphonuclears, 34 per cent lymphocytes, and 6 per cent large mononuclears. A single blood sugar determination showed 79 mg. per cent.

The neurologic examination showed the sense of smell, visual fields, and fundi to be normal. The pupils were right 3,

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left 4 mm., but both reacted well to light and on convergence. There was no nystagmus and extraocular movements were normal. Facial movements and hearing were normal and the bulbar muscles appeared normal to testing in spite of the dysarthria. There was no dysphagia and the pharyngeal reflexes were normal. The biceps, triceps, wrist, knee and ankle jerks were all normal. The plantar responses were normal except for an equivocal Babinski response on the right. Gordon and Oppenheim reflexes were not obtained. The abdominal reflexes were very small. Sensory perception was unimpaired.

Mentally the patient was facetious, slow in cerebration, and slow and ataxic in speech though not aphasic. Disorientation was marked and memory for recent events poor and spotty.

The patient was confined to a sanitarium for observation. From day to day there were marked fluctuations in her mental state. She was repeatedly found in a state resembling intoxication with the facetiousness of drunkenness and with appropriate ataxia. Yet she did not drink. She was also found repeatedly in coma but occasionally she was perfectly normal. On a few occasions fractional epileptiform seizures were observed.

As she had already had neurosurgical investigation for cerebral neoplasm with negative air encephalogram, and electroencephalogram which showed generalized dysrhythmia, these procedures were not repeated. She was thought to be epileptic but a trial with phenobarbital and Dilantin sodium did diminish the incidence of seizures. She still lost consciousness every few days. Blood sugar studies never gave a single reading below 70; a glucose tolerance test was not performed.

On one occasion the patient was in a state of dysarthria and ataxia when she was urged to drink her orange juice. In a few minutes she was normal. Treatment of her coma with intravenous glucose was then tried and it was found possible to revive her in one minute.

The family was urged to have exploration of her pancreas for adenoma. The son was willing but the patient refused any and all surgery. Treatment was continued with emergency glucose and a regular diabetic diet. Her crises could still not be averted. On the other hand, they increased in severity and frequency.

The family was then advised to have the patient declared mentally incompetent and the son appointed guardian. This was accomplished but the son refused to oppose the patient's wishes. An ultimatum was served when the writer predicted death in a few days unless action was taken.

OPERATIVE FINDINGS AND COURSE

Emergency surgery was then performed. It was necessary to remove the spleen and gallbladder in order to gain access to the pancreas, which was surrounded by adhesions. A large adenoma was found and resected. The patient was able to leave the hospital on the thirteenth day and to leave the sanitarium after another 22 days, six months from the time of the initial examination.

At this writing, April 21, 1953, the patient has remained well for a year. She travels about the city alone, is well informed, completely oriented, and as euphoric as on the first visit. She is about to be restored to legal competency.

COMMENT

The lessons to be learned are that hypoglycemia from adenoma of the pancreas comes in episodes resembling alcoholism in many respects and epilepsy in many other respects, that single blood sugar determinations may completely fail to show even critical hypoglycemia, and that successful surgery alone may bring about a cure.

CASE REPORT

Concerning Cerebral Vasospasm

Miller Fisher, M.D.
and Douglas G. Cameron, M.D.

It is not the purpose of this presentation to discuss the nature and pathogenesis of all the cerebral manifestations which are rightly or wrongly attributed to vasospasm. Moreover, a critical examination of the concept of vasospasm and a detailed study of the alternative explanations for transient cerebral phenomena will not be attempted. Rather would we like to present a case report in which some new characteristics of the process are uncovered through the use of anticoagulants and in which the way to a more effective therapy may be pointed.

The patient, an elderly woman, had had many transient cerebral attacks characterized by sudden explained vomiting, weakness of all limbs, more on the right side, and dimmed vision. The later course of events justified the clinical diagnosis of incipient basilar artery thrombosis. After a suitably long period of control observation during which repeated temporary attacks were accompanied by an advancement of the neurologic deficit, anticoagulants were administered and for 33 days there was not a single attack. On cessation of therapy and with return of the prothrombin time to normal, attacks reappeared but again were completely banished by anticoagulants. Then, unknown to the patient, a placebo was given in place of the anticoagulant, and within a few days attacks recurred, in one of which the patient became completely paralyzed and was unable to see, swallow or speak. On resumption of the anticoagulant therapy attacks again ceased entirely, the neurologic signs largely cleared and the patient was satisfactorily carried along at home for a period of four and a half months. Cessation of therapy at the end of this time has not been attended by any untoward effects.

CASE HISTORY

The patient, a woman aged 70, had led an extraordinarily active life intellectually and socially. She retained all her faculties and gave a reliable history. She was admitted to the Montreal General Hospital March 10, 1952 and discharged June 24, 1952. On admission she stated that for about a month she had been having repeated transient attacks described as follows: all power seemed to go out of her body; the right hand and occasionally the right face became numb and in addition there was a peculiar "terrible" sensation in her head. The attacks had been occurring once or twice a day and lasted only a few

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minutes but usually an hour passed before she felt herself again. In addition, during the last three weeks she had three attacks in which the right wrist flexed forcibly and the hand became tight and drawn-up. At the same time numbness around the mouth appeared. She did not lose consciousness in these attacks which lasted five or ten minutes. On closer questioning, the history of illness could be taken back several months.

In the summer of 1951 the patient had complained of transient visual blackouts and had had her eyes examined. In September 1951 a sudden blackness swept before her eyes, she felt weak and could not speak properly on the telephone, although she was able to stand. In November there had occurred an episode of sudden numbness or stiffness around the mouth and she vomited precipitously over the counter of the store in which she was shopping. She became ashen and felt confused for 10 to 20 minutes. Subsequently she had a similar attack. In December she had a five minute attack of numbness of the right side of the body, face, hand and leg.

During December and January she had had two episodes of dizziness and vomiting with an associated feeling as if a wire were being drawn tightly around her forehead. Then the attacks began for which she was admitted to hospital. In these latter there was no dizziness or vomiting. There had been no dysphasia, convulsions or headache. Detailed neurologic examination ten days prior to admission had shown no abnormality.

Previous illnesses included an appendectomy and cholecystectomy in 1926, which were followed by a large ventral hernia. She had been aware of hypertension for several years. An electrocardiogram in January 1952 had shown changes typical of an anterior myocardial infarction. The patient did not smoke or drink.

Examination: Temperature, pulse and respiration, normal; blood pressure 205/105; sallow complexion; well nourished; moderate cardiac enlargement, sounds clear, normal rhythm. Neurologic examination including cranial nerves, motor power, sensation, reflexes and coordination were not remarkable. Mentality: she was alert, intelligent and of good memory.

Laboratory studies: Hemoglobin was 88 per cent, blood count, normal; urinalysis was repeatedly normal. Roentgenograms of the skull were not contributory, while one of the chest showed cardiac enlargement. An electrocardiogram showed no change from that of January 1952.

Course in hospital: The course of events is best shown in the form of a diary. In numerous attacks the blood pressure and pulse were carefully and repeatedly checked but no important change was found, i. e., a measurable alteration in the systemic blood pressure did not seem to accompany the attacks.

March 10 – Admitted. *March 12* – Mild weak spell while taking breakfast. *March 13* – Brief attack of numbness in right hand. *March 14* – 2:30 a.m. – complained of numbness in right hand, and right side of face. 8:30 a.m. – slight attack marked by slurring of speech. *March 15* – Numbness of right hand and face for brief period. *March 16* – 5:30 a.m. – numbness of right side of body including lower face, neck, right hand, right side of trunk and right foot. The right hand became so weak she could not use it for lifting herself up in bed, for combing her hair or writing. Mentally, she remained alert. This attack failed to clear completely and 36 hours later the hand was weak and the right side uncomfortably prickly. The tendon reflexes were brisker on the right side and the right plantar reflex was not so promptly flexor as on the left. *March 23* – Right leg felt weak. 4:00 p.m. – numbness of lips and adjacent face. Patient felt weak and speech was slurred – felt better in half an hour. *March 24* – Complained of difficulty in swallowing. *March 25* – Attack of weakness and inability to move right arm. Choked on swallowing pill. Dysphagia persisted. *March 26* – Weakness of right side – very listless – nauseated. *March 27* – She awakened in morning with difficulty in swallowing and speaking, and her right side felt weaker and more numb. She sat up in a chair and became quite weak, having difficulty in using both lower limbs. 7:00 p.m. – examination showed weakness of right hand and sensation more impaired than previously. The tendon reflexes were all brisk and there was a Babinski response bilaterally. The right side of the tongue was weak; the ocular movements were not abnormal. Handwriting was illegible. *March 28* – Awakened feeling well but at 10:00 a.m. there began an attack lasting half an hour in which all limbs felt very weak, the right-sided weakness being accentuated. On examination both hands were weak, speech was slurred and a Babinski sign was again

present bilaterally. She remained mentally clear and said that the episode was a most uncomfortable one, particularly the sensation within the head.

Comment: It was apparent that although the worst symptoms were transient, a persisting neurologic deficit was accumulating. Roniacol 50 mg. three times a day had not altered the course of events. The clinical diagnosis was thrombosis of the basilar artery and in order to stop the process, anticoagulant therapy was started. Danilone (Phenylindandione, PID) 200 mg. was prescribed. Heparin 50 mgm. intramuscularly every four hours was given in addition, for the first 24 hours. Medication was not otherwise altered.

March 28 to May 1 – The prothrombin time (Quick) was maintained at about twice the control value. During this period there was no single transient episode of any sort. She was able to be up, walking by herself, writing letters, and so on. However, the right leg was somewhat spastic, sensation in the right hand had remained impaired and the right plantar response was still extensor. Speech was quite normal unless she was tired. Swallowing was not impaired. *May 1 to May 5* – The anticoagulant dosage was decreased and by May 2 the prothrombin time was about normal. *May 5* – Prothrombin time normal. 8:00 a.m. – sudden blurring of vision lasting only a few seconds associated with slight nausea. The visual disturbance was the same as she had had during previous transient attacks. 11:00 a.m. – while sitting, patient became weak and could not stand or support herself. There was a "terrible" feeling in her head. Vision was blurred, there was slight nausea, speech became slurred and the right hand became numb. She complained of feeling very cold. Within half an hour she felt better. 3:00 p.m. – attack lasting but a few seconds, with blacking out of vision and numbness around the mouth. The right hand definitely felt more numb than it had in the last few weeks.

Comment: There having been three attacks in one day, it was decided to give PID therapy again, with heparin for the first 24 hours, while the future plans for therapy could be discussed.

May 5 to May 20 – Anticoagulant therapy – no attacks whatsoever.

Comment: As the patient lived in a village where facilities for measuring the prothrombin time were not available, it was decided to try once more to withdraw anticoagulants before sending her home. Since withdrawal the first time had resulted in a recurrence of symptoms and as the patient feared another return of symptoms she was given a placebo pill.

May 21 – An almost identical placebo pill was substituted for PID and the prothrombin time fell to normal by May 24. *May 24* – on awakening, the right side felt more numb than usual. At 11:30 a.m. vision suddenly became blurred and the head sensation she had experienced previously reappeared. Speech became slurred, the right side of the face became numb and the patient felt weak all over. She lay down and believed she got relief immediately. Two hours later the attack had cleared, for neurologic examination showed only the traces of deficit present on March 28th, except that sensation in the right hand had returned to normal. *May 25* – A very good day. *May 26* – Awakened with increased numbness of right arm and slurred speech. 11:30 a.m. –Patient was sitting up talking to visitors when she said her face felt numb on the right side. Speech became slurred and she could not swallow. She looked pale. In a few minutes she could scarcely talk at all and said she could hardly see her visitors. She lay down and in about 20 minutes she could see well again. However, numbness of the right face, arm and leg persisted longer. The patient mentioned a left-sided headache.

Comment: It was decided that there was little doubt that anticoagulant therapy was helping to prevent attacks of paralysis and that it was not justifiable to withhold therapy any longer. Therefore, heparin was started immediately in 50 mg. doses intramuscularly every four hours and unlike previous occasions only three doses were given at 3:00, 7:00 and 11:00 p.m. PID was restarted also. *May 27* – No attacks – prothrombin time 27 sec. (normal 20). *May 28* – Prothrombin time 25. Patient awakened feeling very weak and without appetite. By mid-morning the right side was almost completely paralyzed (face, arm and leg) and the left arm and leg were much weaker than usual. The right side felt numb and the left leg jerked uncontrollably. Vision was impaired so she could not see an attendant. Speech became slurred at first and later was lost entirely. Swallowing became increasingly difficult and finally at noon the patient could not swallow any water and on sucking through a straw, air passed through the nose. From time to time

she complained of bursts of frontal headache lasting only a few moments. The attack reached its peak at 2:30 p.m., the patient being unable to move even her head but shortly thereafter improvement began. At 6:00 p.m. speech was still slurred and both sides of the body were weak, the right more so. Swallowing was extremely difficult, a single teaspoon of water requiring four or five swallowing movements which were followed by a slight cough. Vision had returned to its former state. Apparently the patient remained mentally clear throughout the attack. There was no dizziness or diplopia. Examination at 6:00 p.m. showed both hands weak, a right facial weakness, swallowing as above, speech slurred and appreciation of pin-prick impaired on the left side. All tendon reflexes were brisk and there was a prompt Babinski response bilaterally. Intramuscular heparin therapy was begun immediately, and continued for 24 hours, PID of course being maintained.

Subsequent course (May 28 to November 15): Improvement was surprisingly quick. Within a few days speech was no longer slurred and in one week swallowing was almost perfect. The motor power of the limbs gradually improved and in two weeks was about the same as before the last attack. Walking with a cane was resumed. PID therapy was maintained and there was no further episode of transient worsening. Anticoagulant medication was stopped November 15, 1952, and the patient's course has been uneventful up to the time of writing. The patient is at home and feeling quite well except for spasticity of the right leg which restricts her walking.

DISCUSSION

If it is agreed that in the present instance the periodic transient episodes were typical of the vasospastic phenomena which herald the onset of some strokes, then it follows that the process of vasospasm has been altered and even prevented by anticoagulant therapy. Indeed it seems likely that the process in this case was related to the mechanism of coagulation or thrombosis of blood rather than to transient changes in the caliber of cerebral arteries. Of course it is not implied that all cases of vasospasm have a similar pathogenesis, for our experience at present indicates that there probably are several different mechanisms.

In trying to explain the events in this case, it is difficult to picture exactly a process which could lead to transient cerebral attacks and yet be prevented by anticoagulant therapy. Prodromal symptoms are very common in thrombosis of the basilar artery, the tentative diagnosis in the present case. Pathologically in such cases it is usual to find an older region of atherosclerotic deposit with superimposed thrombus in the lower portion of the artery or in each vertebral artery, while a more recent reddish black column of blood tightly fills the upper portion of the basilar artery. The appearance suggests that the clot has grown progressively upwards until the vascular supply to the pons has become excluded from the collateral flow via the Circle of Willis and other branches. As stated above it is far from clear how transient phenomena are evoked by such a pathologic process. The fact that heparin was as effective as PID indicates that hindrance of coagulation or thrombosis was the important factor in prevention of the attacks.

If the earliest stages of the clotting mechanism are linked to the transient episodes of ischemia, several possibilities regarding the pathogenesis of the latter quickly come to mind. It is conceivable that agglutination of platelets or erythrocytes could temporarily block the mouths of small penetrating branches or impede blood flow through narrow collateral channels. It is possible, though unlikely, that a clot could precipitate local vasoconstriction. However, further speculation is not warranted from the data presently at hand.

From a therapeutic viewpoint it is likely that the use of anticoagulant therapy in this case enabled the patient to survive what threatened to be a most

serious stroke. It was hoped that prolonged anticoagulant therapy would so alter the pathologic state that clotting would not be resumed when anticoagulants were stopped or that additional collateral flow had become available. The patient's future course may help to reach a conclusion in these matters.

The possibility that such therapy will prove beneficial in similar cases is a very important one, for at present there is no particularly effective treatment for cerebrovascular disease. Moreover, if improved therapy is to be achieved, it is logical to bring it to bear before permanent paralysis has occurred, that is, at the time when transient prodromal warnings are occurring.

It is our impression that transient phenomena preceding the onset of a stroke are much more frequent than is commonly believed, for the patient often neglects them, while his physician does not inquire about their occurrence once paralysis has occurred. In the field of cerebrovascular disease transient episodes nearly always reflect a thrombotic process, for intracerebral hemorrhage and cerebral embolism almost never occasion prodromal symptoms. A leaking berry-aneurysm not infrequently causes a few transient episodes, but a careful history, the presence of severe headache and bloody cerebrospinal fluid allow an accurate diagnosis in the early stages. Occasionally cysts of the third ventricle or cerebral tumors produce temporary symptoms, but again the total clinical picture should allow a differentiation from vascular disease. During the past few years all cases of stroke seen by the authors have been specifically questioned concerning warning phenomena. In the majority of cases of cerebral thrombosis there had been at least one such attack, while many had had numerous episodes (25 to 500) before the final arrival of paralysis. In the same category as far as the present type of therapy is concerned are those cases in which the first fragment of paralysis appears several days before the onset of the major stroke.

There is not space here to consider in detail the problem of cerebral thrombosis. No cerebral vessel seems to be immune but those most commonly affected include the basilar, vertebral, internal carotid, posterior cerebral, anterior cerebral, middle cerebral and perforating arteries. The vast array of warning symptoms reflects this wide distribution of vascular disease. These include paralysis, paresthesia, slurred speech, dim vision, dysphagia, agnosia, speechlessness, unconsciousness, falling, jerking of limbs, dizziness, diplopia, monocular blindness, headache, head noises, confusion, disorientation, depression and the picture of senile dementia. Typical seizures are rare except as a coincidence. Transient symptoms seem to occur at any time of the day or night, whereas persisting fractions of a progressive hemiplegia usually occur during sleep.

It is important to realize that not all transient attacks finally end in a major stroke with persistent disability. In a recent case approximately 50 attacks of left hemiplegia lasting ten to 15 minutes preceded the onset of a severe paralysis from which the patient recovered almost completely in a few weeks We have encountered many other similar although less striking examples At present, however, we are inclined to fear the worst in each case, particularly where an objective neurologic deficit is accumulating or where speech and intellectual function may be affected. Anticoagulant therapy is being used not only in such cases of vasospasm but in other cases of early cerebral thrombosis in which a clear cut advance in symptoms and signs has occurred over a period of 24 or 48 hours. Results are highly satisfactory but few cases are seen by a neu-

rologist at the stage of prodromal attacks so that a further appraisal of anticoagulant therapy awaits earlier discovery of these patients. To be balanced against any efficacy of anticoagulants is the danger of such therapy. Hemorrhage is the only real threat and if the prothrombin time is repeatedly checked until the patient's tolerance is known, accidents should be prevented.

One further point should be mentioned. A not infrequent type of stroke is the small rather evanescent one associated with hypertension. Although atherosclerosis is always present, the exact pathogenesis of the vascular occlusion is not known although thrombosis is suspected. Some of the lesions at autopsy show abundant blood pigment bespeaking a small hemorrhage. Because of the uncertainty of the nature of this lesion coupled with the fact that altering the coagulability of the blood might predispose to massive hypertensive intracerebral hemorrhage, severely hypertensive patients are treated with anticoagulants only after a special consideration of the pros and cons.

SUMMARY

A case is presented in which attacks of cerebral vasospasm were clearly prevented by anticoagulant therapy, and in which the patient survived a severe stroke with little residual disability. The significance of anticoagulants in the treatment of cerebral thrombosis in general is discussed briefly.

The onset of some attacks is attended by a well-known scream, the "epileptic cry." It is more frequently absent than present. Its characters vary. The true epileptic cry is a wild, harsh, screaming sound, probably due to the tonic spasm of the thoracic and abdominal muscles expelling air through the glottis, narrowed by spasm. The sound has been compared by Reynolds to the "cry of a distracted peacock." It is indeed scarcely imitable except by the larynx of a bird. There is a parrot at the country branch of the Hospital for Epilepsy which has learned to imitate the cry so closely as frequently to deceive the nurses, who run to the spot, expecting to find a patient in a fit. In many cases the cry is not of this character, but is a simple scream, sometimes repeated once or twice, as the fit is coming on. No recollection of the cry is, as a rule, retained. In rare cases the patient is conscious of the scream, although he is unable to prevent it. Reynolds has recorded an example of this, and I have met with one or two instances.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CASE REPORT

Aneurysm in the Third Ventricle

Lloyd J. Lemmen, M.D. and Richard C. Schneider, M.D.

The following case appears to be of sufficient rarity and clinicopathologic interest to warrant publication.

CASE REPORT

An eight month old white boy was noted to have an enlargement of his head two months before admission to University Hospital on January 2, 1952. Pregnancy and delivery had been normal, as had been development until the enlargement of the head was noted.

Examination revealed a well developed infant who weighed 22 pounds and 15 ounces, measured 29½ inches in height, 26 inches in head circumference (birth measurement 14 inches), and 18½ inches in chest circumference. The head was hydrocephalic; the facies were normal. Anterior and posterior fontanelles were open and were normal to palpation. Neurologic examination disclosed no abnormality. Roentgenograms of the skull revealed general enlargement of the cranium and increased digital markings of all the cranial bones.

On January 8, 1952, a right ventriculogram was done under Avertin anesthesia. The ventricular pressure was 180 mm. of water, and 170 cc. of ventricular fluid was removed. This study revealed symmetrical massive dilatation of the lateral ventricles, and air in the anterior third ventricle outlined an obstruction in this ventricle (figure 1A).

On the same day a right parietal osteoplastic craniotomy was performed. The lateral ventricle was entered at a depth of 0.5 to 1 cm., and the choroid plexus could be seen displaced laterally and forward by

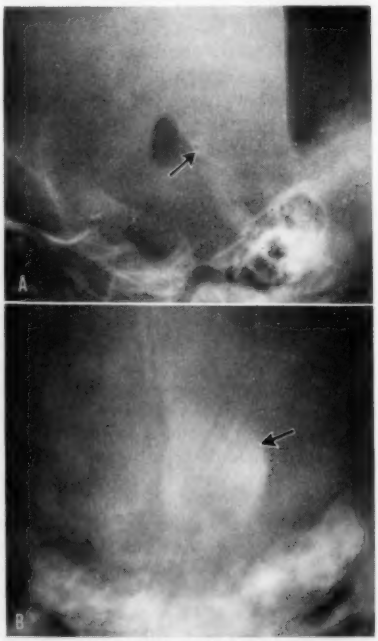

FIG. 1. A. Ventriculogram (brow down) showing space-occupying lesion in posterior third ventricle. B. Frontal arteriogram showing aneurysm in midline outlined by dye.

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a mass in the posteromedial wall of the ventricle. An incision was made into what was thought to be the right thalamus and a mass was encountered which was covered by a yellowish-gray, glistening membrane. As this membrane was being cauterized in preparation for the insertion of a needle, the tip of the coagulating forceps penetrated it and marked arterial bleeding occurred. Hemorrhage was controlled by Oxycel and the procedure terminated.

On January 15, 1952, a right common carotid arteriogram revealed upward and anterior displacement of the anterior cerebral artery, including pericallosal and callosal marginal vessels. There was spreading of the Sylvian vessels. Both posterior cerebral arteries could be differentiated from the posterior communicating artery. The anterior choroidal artery was seen to be displaced dorsalward and anteriorly. In the frontal view in a late arterial phase of dye injection an area of increased density 2 cm. in diameter could be identified in the midline (figure 1B).

Three days later a third ventriculostomy was performed. The lamina terminalis was opened above and below the optic chiasm.

Postoperatively the patient developed decerebrate rigidity, and death occurred on February 28, 1952.

Necropsy revealed a brain with far advanced hydrocephalus. An aneurysm, measuring 4 cm. in diameter, was found in the posterior portion of the third ventricle. It contained a multi-laminated blood clot. The operative site was covered with Oxycel at the point of penetration in the wall of the aneurysm. The basilar artery had an anomalous course to the right of the midline. The two posterior cerebral arteries passed laterally from the bifurcation of this laterally placed basilar artery, and after receiving the posterior communicating arteries they wound around the cerebral peduncles to a point between midbrain and thalamus. At this point, cortical branches of the posterior cerebral artery passed laterally to temporal and occipital lobes, while a single branch from each posterior cerebral artery passed between the pulvinar of the thalamus and superior quadrigeminal body into the posterior dorsal aspect of the aneurysm. A small vessel passed forward on the right lateral wall of the third ventricle from the anterior wall of the aneurysm (figure 2).

DISCUSSION

Obstructive hydrocephalus secondary to vascular abnormality in the third ventricle has been observed in children by Matson[1] and others. The location and size of this aneurysm precluded surgical excision.

This vascular lesion probably had its origin in early embryonic life. Padget[2] found, in the embryos of 7 to 12 mm.,

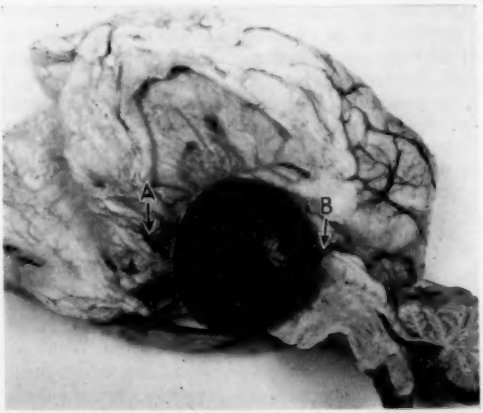

FIG. 2. Paramedian section of the brain showing branch of posterior cerebral artery (B) entering aneurysm. A small vessel (A) passed forward on the right lateral wall of the third ventricle from the anterior wall of the aneurysm. The frontal lobe has been drawn upward and forward.

that from the caudal end of the posterior communicating artery a large branch (diencephalic artery) supplied the developing diencephalon. The posterior choroidal artery, which is more anteroventral of two large branches of the diencephalic artery, terminates in older embryos in the choroidal infoldings at the diencephalic roof, and here anastomoses with the ipsilateral anterior choroidal artery; the other branch courses toward the pineal primordium. Unresolved vestiges of anastomoses between these primitive vascular channels and those of the opposite side resulted in the formation of this aneurysm.

CONCLUSION

A congenital aneurysm involving branches of both posterior cerebral arteries is reported. Clinically the lesion manifested itself by an obstructive hydrocephalus of the third ventricle.

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We have seen that in a certain proportion of cases the megrim paroxysms terminate spontaneously in vomiting, and in a few individuals are indefinitely prolonged until vomiting occurs; hence Emetics have been frequently employed with the view of anticipating this spontaneous termination, but with very uncertain success. In the blind form of megrim Heberden says they do no good and may do harm,—"Vomitus parum aut nihil juvat; sunt qui putant eum nocuisse." Dr. Airy tried an emetic in his own case, but without benefit. Fordyce, on the contrary, says that "emetics have sometimes a most favorable effect. Lepois, who suffered for thirty years of his life, generally got relief when he could produce vomiting." Tissot refers to instances both of useful and useless vomiting, and he says that some patients derive benefit from whatever promotes it, as warm water. He occasionally prescribed ipecacuanha in emetic doses, but chiefly as a corrective of gastric disorder, especially in conditions of atony attended with the production of glairy mucus.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Neurology BOOK REVIEWS

Commotio Cerebri. Cerebral Concussion and the Postconcussion Syndrome in Their Medical and Legal Aspects

Cyril B. Courville, M.D. 1953. Los Angeles: San Lucas Press. 161 pages. $5.25.

This delightful little book is one of a series of related studies which the author is contemplating. The volumes will constitute a comprehensive review of head trauma which will find a welcome place in the library of many physicians and surgeons. In this monograph the author and publisher have combined to produce an authoritative and easily read account of cerebral concussion through the ages.

In the legends of prehistoric people and in the folklore handed down from generation to generation, Courville finds references to cerebral trauma with loss of consciousness, evidence that primitive peoples knew, not only of the immediate effects of a head injury but also of its after effects. In ancient written history, the varied results of blows to the head are even more accurately described so that the syndromes of concussion, contusion and compression may be recognized. Many notable figures in history, Courville found, have suffered from concussion as the result of a civilian accident or military coup.

In the chapter on "Mechanism of Concussion," Courville reviews the concepts of the traumatic loss of consciousness from ancient times to the present emphasizing the modern rediscoveries of theories, centuries old. The role of the cerebral circulation in the postconcussion syndrome, Courville believes, has not been sufficiently emphasized in the past. One would agree that many phenomena which may be due to circulatory disturbance are not adequately explained by present hypotheses. In the chapter on cellular pathology, Courville states that pathologic lesions may be due to (1) the general effect of the concussion producing alterations in the neurone, (2) multiple focal effects which appear to be the results of local ischemia (vasospasm) or of a prolonged drop in blood pressure, or (3) structural alterations due to edema of the brain.

The postconcussional syndrome which the author believes has an organic substrate is well described. For the prevention of this syndrome Courville seems to favor long periods of bed rest – a form of treatment not fashionable in neurosurgical circles these days. In the chronic postconcussional state, it would seem that medicinal therapy is scanty and psychotherapy of doubtful value.

The book is illustrated with 12 figures. Appended is a selected list of references covering particularly the American, English, German and French literature. The general format of the book is pleasing; the type is easy to read. The author's

concise style with his occasional pithy comments makes for clear and interesting reading. While the argument is not very critical and, at times, the author seems to be biased in his selection of material, the presentation is generally accurate.

The book is an excellent review of the subject from prehistoric times to the present and can be recommended to all neurologists, neurosurgeons and general practitioners. Medical historians will find in it much interesting material. All who read it will await the subsequent volumes with interest. A.E.W.

Principles of Neurology in the Light of History and Their Present Use

Walther Riese, M.D. 1950. New York: Nervous and Mental Disease Monographs (No. 80). 177 pages, $6.00.

The pressure of everyday practical demands tends to confine the neurologist's attention to these immediate problems. It is easily forgotten that the body of experience and knowledge referred to as neurology is much larger than any catalog of the signs and symptoms of disease, of the reflexes which one notes, of the classified diagnosis which one makes, and of the treatment which one proposes. The broader horizons of neurology are thus apt to be left unperceived.

In this monograph Walther Riese reaches beyond these operational confines of iatromechanical neurology and discusses the basic theoretic postulates and propositions of neurology as they have developed since the end of the eighteenth century. As a historian of neurology Dr. Riese is particularly competent to place in proper perspective the movement of ideas which have shaped the theory of neurology during the past 150 years and which continue to influence new neurologic thought. The major theoretical propositions of modern neurology have emerged from the work of Hughlings Jackson, Sherrington, Head, Goldstein and von Monakow and of their forerunners and followers.

The author begins with the discussion of the "basic scheme" of the concept of reflex arc, and goes on to the concepts of integrative action, of the hierarchy of the Jacksonian levels of function, of inhibition and of resistance. In chapters on evolution of nervous functions, progressive cerebration, lateral dominance, regional vulnerability, dissolution of functions, diaschisis, restitution and substitution of functions and on the role of the momentum of lesion, the author submits the prevailing notions on cerebral localizations to a penetrating critique.

The monograph is written as "a contribution to neurological thought rather than to experiential research." Its reading requires a considerable intellectual tension and patience to be profitable, but those who have it will be rewarded by a challenging vista of broader horizons in the study of the organization and meaning of the function of the nervous system in the ease and disease of living. P.I.Y.

Neurology

Lobotomy and Epilepsy

A Study of 1000 Patients

Walter Freeman, M.D., Ph.D.

PENETRATING wounds of the brain are a frequent cause of post-traumatic epilepsy. The subject has been reviewed in detail by Walker[1] and recently by Watson,[2] the latter finding an overall incidence of 41.6 per cent. The longer the interval between injury and follow-up, the greater the cumulative incidence of seizures, although in the latter stages the number of new cases tends to be balanced by those who remain free from seizures. Meyer[3] reported 33 cases of gunshot wounds of the brain in which seizures developed eight or more years after injury. Injuries of the type described, mostly incurred in war, are apt to be much more extensive and complicated than those incurred during lobotomy. Complications such as infection, foreign bodies, laceration of blood vessels and subsequent cranial defects undoubtedly increase the incidence of post-traumatic epilepsy. It was therefore considered worthwhile to study the occurrence of post-taumatic epilepsy in patients undergoing lobotomy. Here the location and extent of the operation are known, the cortical injury is small, the bony defect is minimal, and the incidence of complications in the form of hemorrhage and infection is low.

The occurrence of convulsive seizures in 25.6 per cent of patients after prefrontal lobotomy shows that the problem is a serious one.

From the department of neurology and neurological surgery, George Washington University, Washington, D. C.

Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 10, 1953.

MATERIAL AND METHODS

Six hundred and twenty-two patients subjected to prefrontal lobotomy have been followed for a minimum of two years and some for more than 15 years. The method of follow-up has been for the most part (80 per cent) personal interview and interview with relatives. In other instances the written reports of patients, relatives and hospital or family doctors have been acceptable. Follow-up was seriously conducted and no patients were lost in the investigation even though some of them were no longer in this country.

Most of the prefrontal lobotomy operations were performed by Dr. James W. Watts, but a few were done by Dr. J. Peter Murphy. Some patients had been operated upon elsewhere before coming to Washington for a second lobotomy.

For comparison, a group of 498 patients treated by transorbital lobotomy was included in the study. Dr. Watts performed six of these operations; Dr. Jonathan M. Williams performed 57, and the rest were done by the author or under his guidance. These patients have been followed with one exception for a year and many of them for from two to seven years, but the long-range follow-up like that of the prefrontal series will take time, since the transorbital series was begun only in 1946, ten years after the prefrontal operations were initiated.

All patients who had seizures were included in the statistics, even if the convulsions were observed only in the immediate postoperative stage. The patterns of seizures and their response to medication were so complicated that no useful information was forthcoming. The lesions were all situated in a relatively constant area of the brain, so that the factor of localization was narrowed to various parts of the frontal lobe. Other factors of significance were operative complications, multiple operations, previous epilepsy and other organic diseases of the brain, and preoperative application of convulsive shock therapy.

RESULTS

The lowest figure, percentagewise, was obtained in patients operated upon only once, with no complications, and free from preexisting brain disease or epilepsy. This figure was 19 per cent for prefrontal lobotomy and 1 per cent for transorbital lobotomy. The highest incidence was in patients with both preexisting brain disease and operative complications, lobotomized two or more times. In seven such patients treated by prefrontal lobotomy, the incidence of seizures was 86 per cent. There was only one such patient in the transorbital series and no convulsions have been reported yet. From these figures it may be concluded that the extent of damage to the cerebral cortex is the outstanding factor in the development of convulsions.

Fourteen patients in the prefrontal series and 11 in the transorbital series had epilepsy previous to lobotomy. In these cases the operations were performed for the relief of disturbed behavior that rendered the patients danger-

TABLE 1

EFFECT OF LOBOTOMY ON PATIENTS WITH AND WITHOUT PREOPERATIVE CONVULSIONS

Convulsions:	*Prefrontal Lobotomy*		*Transorbital Lobotomy*	
	Number	*Per cent*	*Number*	*Per cent*
None before—none after	434	73	411	96
None before – present after	143	24	8	2
Present before – none after	*3	1	*8	2
Present before – present after	11	2	2	0.5
Total	591	100	429	100

*See Appendix.

ous to themselves or others. The distribution of preoperative and postoperative convulsions is shown in table 1. It will be seen that in some cases the operation appears to have had an arresting effect upon convulsions. This feature will be studied later in more detail.

EFFECT OF PREOPERATIVE SHOCK THERAPY

Convulsive shock therapy is sometimes followed by spontaneous convulsions. These have been studied by Liebert[4] and others. The incidence is about 1 per cent and the convulsions appear to be of a benign type, tending to disappear even without medication. Only one of the patients experiencing convulsions before but not after lobotomy belongs in this group. The effects of shock therapy upon postoperative seizures is shown in table 2. The incidence of seizures is not significantly increased by preoperative shock therapy. These findings are in agreement with those of Feuillet et al.[5] who state: "The pathogenic role of seismotherapy remains rather dubious."

TABLE 2

EFFECT OF LOBOTOMY ON PATIENTS WITH AND WITHOUT PREOPERATIVE SHOCK THERAPY

	Without Shock Therapy				*With Shock Therapy*			
	Prefrontal		*Transorbital*		*Prefrontal*		*Transorbital*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions after lobotomy	31	22	0	0	83	25	7	2
No convulsions after lobotomy	112	78	73	100	253	75	314	98
Total	143	100	73	100	336	100	321	100

Preoperative epilepsy, organic brain disease and operative complications omitted.

EFFECT OF SOMATIC DISEASE

Most of the patients in this series were operated upon because of mental disorder, but a smaller number, presumably mentally normal, were operated upon for the relief of pain. The results are shown in table 3. There is no difference.

TABLE 3

EFFECT OF LOBOTOMY ON PATIENTS WITH AND WITHOUT PAINFUL SOMATIC DISEASE

	Pain Cases				*Mental Cases*			
	Prefrontal		*Transorbital*		*Prefrontal*		*Transorbital*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions after lobotomy	4	22	1	4	150	26	9	2
No convulsions after lobotomy	14	78	23	96	422	74	411	98
Total	18	100	24	100	572	100	420	100

EFFECT OF OPERATIVE AND POSTOPERATIVE COMPLICATIONS

Just when a patient is said to have operative or postoperative complications is a matter of judgment. In cases of prefrontal lobotomy, the operative note quite frequently reads that more bleeding was encountered than usual. Since the patients were usually up and about within four days and discharged in a week, such incidents can hardly be called complications. As a rule of thumb, we agreed to call it a complicated case when the patient had to stay in the hospital beyond ten days. This criterion was applicable even in patients in mental hospitals. They could usually be moved from the surgical ward to their own ward within a week, but sometimes stayed on for treatment of their physical condition.

In the case of transorbital lobotomy the period of surgical convalescence was considered to be one day, and only complicated cases were kept longer on the surgical ward.

Operative complications included hemorrhage, infection, paralysis and prolonged inertia. The effect of these complications upon the later development of convulsive seizures is shown in table 4. In this study are included all convulsions except those occurring on the operating table. The presence of operative and postoperative complications with transorbital lobotomy increased greatly the prospect of postoperative convulsions. There was a corresponding increase in prefrontal lobotomy cases from 24 per cent to 30 per cent.

TABLE 4

EFFECT OF OPERATIVE AND POSTOPERATIVE COMPLICATIONS ON INCIDENCE OF CONVULSIONS AFTER LOBOTOMY

	Complications				*No Complications*			
	Prefrontal		*Transorbital*		*Prefrontal*		*Transorbital*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions after lobotomy	16	30	2	20	114	24	5	1
No convulsions after lobotomy	38	70	8	80	365	76	387	99
Total	54	100	10	100	479	100	392	100

Preoperative epilepsy and organic brain disease excluded.

EFFECT OF MULTIPLE OPERATIONS

When the second edition of the monograph was being prepared by Freeman and Watts,[6] the incidence of seizures was known to be much greater following multiple operations. The figures rose in uncomplicated cases from 7 per cent to 47 per cent. This is a logarithmic rather than an arithmetic increase and deserves particular study because of the theoretical and practical aspects of the problem. In performing prefrontal lobotomy the aim is always to operate in such a manner that the patient will experience the best chance of recovery. In patients showing predominantly affective disturbances a conservative anterior operation is preferred; in chronic schizophrenic patients a radical operation gives best hopes of improvement. Too conservative an operation is useless; too extensive an operation is ruinous. The surgeon may have more than one chance to operate upon a patient, but he does so at increased peril of later convulsive seizures. The results of this study are given in table 5. The incidence of convulsions in a "cleaned-up" series of 479 prefrontal lobotomy cases, that is with pre-existing organic brain disease and operative complications excluded, now, an average of more than five years after performance of lobotomy is 19 per cent. When multiple operations are performed (57 double, 7 triple) the incidence of seizures is increased to 53 per cent. The incidence is therefore more than doubled, and this reflects the greater degree of cortical injury. Since the secondary lobotomy was almost always bilateral this means that four cortical penetrations were made through the convexity, and that other penetrations may have occurred on the medial surface or at the base. The corresponding figures on transorbital lobotomy (followed an average of three years) is 1 per cent for a single operation and 3.5 per cent for multiple operations.

TABLE 5

EFFECT OF SINGLE AND MULTIPLE LOBOTOMIES ON INCIDENCE OF CONVULSIONS

	Single Lobotomy				*Multiple Lobotomies*			
	Prefrontal		*Transorbital*		*Prefrontal*		*Transorbital*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions after lobotomy	80	19	4	1	34	53	1	3
No convulsions after lobotomy	335	81	359	99	30	47	28	97
Total	415	100	363	100	64	100	29	100

Preoperative epilepsy, organic brain disease and operative complications omitted.

These figures may be revised later because of the shorter period of time that the transorbital lobotomy patients have been followed, but corroborative evidence comes from the field of electroencephalography, which shows few of the changes reported so frequently following prefrontal lobotomy.

EFFECT OF MULTIPLE COMPLICATIONS

The worst possible complications as far as the development of convulsions after lobotomy would consist theoretically in a combination of preoperative organic brain disease, operative or postoperative complications and multiple operations. The fact that any patients escape convulsions after this combination may be considered remarkable. The results are shown in table 6. The chances are about equal that such a patient will develop seizures after a single prefrontal lobotomy and six to one after repeated operations. There are too few cases in the transorbital series to permit conclusions.

TABLE 6

EFFECT OF SINGLE AND MULTIPLE LOBOTOMIES IN PATIENTS WITH PREOPERATIVE BRAIN DISEASES AND OPERATIVE COMPLICATIONS

	Single Lobotomy				*Multiple Lobotomies*			
	Prefrontal		*Transorbital*		*Prefrontal*		*Transorbital*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions after lobotomy	4	50	0	0	6	86	0	0
No convulsions after lobotomy	4	50	1	100	1	14	0	0
Total	8	100	1	100	7	100	0	0

EFFECT OF LOCUS OF LOBOTOMY

In an effort to find what operation was safest, most effective and least damaging, a large variety of lobotomy operations were undertaken by Freeman and Watts in the developmental period. Detailed records show that a total of some 20 variations were tried. Some of these were abandoned as ineffective, like the original Moniz procedure; others like the revised Moniz procedure (making cores in the inferior part of the frontal lobes) proved to be too dangerous. It is hardly worthwhile to present a study of all the various types, since the percentage figures would sink into insignificance. Table 7 indicates the incidence of seizures in uncomplicated cases after several of the more commonly performed operations. A brief description of these will show that the closer to the motor cortex the operations of lobotomy are carried out, the greater is the incidence of seizures. This fact has also been noted by Scoville[7] in comparing the incidence of postoperative epilepsy following undercutting in the basal, polar and medial regions, and more especially by Pool.[8] Topectomies involving the superior convexity carried an incidence of 20 per cent, those at the pole an incidence of 17 per cent and those in the orbital region an incidence of 10 per cent. These figures are subject to revision when these patients have passed the five year mark.

The Moniz lobotomy and Moniz revised were carried out through burr holes close to the coronal suture, 3.5 cm. from the midline. With minimal trauma to the cortex a leucotome with a cutting blade was introduced into the

TABLE 7

EFFECT OF LOCUS OF SINGLE LOBOTOMY ON INCIDENCE OF CONVULSIVE SEIZURES

Type of operation	*Total Number*	*With Convulsions Number*	*Per cent*
Moniz	8	1	38
Moniz, revised	2	1	50
Anterior	16	3	19
Lower quadrants	53	7	13
Standard, omit stabs	55	7	11
Standard, with stabs	160	22	14
Radical, 5-10 mm. posterior, parallel to suture	24	12	50
Radical, 5-20 mm. posterior, slanting forward	7	2	28
Radical, through suture, slanting posteriorly, 5-20 mm.	90	25	28
Transorbital, simple	185	2	1
Transorbital, medium	108	1	1
Transorbital, deep	101	2	2

Preoperative epilepsy, organic brain disease, and operative complications omitted.

depths of the frontal lobe and six cores were cut, each about 1 cm. in diameter. It happened occasionally that small vessels were caught by the leucotome and were found clinging to the instrument. On two occasions the blade of the instrument broke and had to be extracted through an enlarged cortical incision. Neither of these cases was complicated by undue hemorrhage. The revised Moniz operation was carried out in the same manner except that nine cores were cut in the more basal portions of the frontal lobe.

Anterior prefrontal lobotomy was carried out through burr holes placed about 1 cm. anterior to the coronal suture and 6 cm. above the zygoma. The incisions were made in the frontal lobes through the second frontal convolution (area 46) and carried inward toward the base, and upward toward the convexity.

Lower quadrant lobotomy was performed through the coronal suture 6 cm. above the zygoma, but the incision was not prolonged above the free margin of the falx cerebri. The fibers at the base were rather completely transected by this operation. The plane of section in all these prefrontal lobotomies was checked by roentgenograms with iodized oil injected into the incisions.

The standard lobotomy was carried out through similar holes and the leucotome was used to cut a quadrantic area in both upper and lower quadrants of the frontal lobe. This was often found to be insufficient so that in later cases the incisions were deepened to the midline and the free margin of the sphenoidal bone by means of the radial stab incisor. The standard operation practically always penetrated into the ventricles, and in addition usually severed the frontal operculum and anterior part of the insula.

Radical operations were performed through a superior approach, 3 cm. from the midline. Sometimes the holes were moved back as much as 2 cm.

behind the coronal suture and the incisions in the frontal lobe were angulated forward so as to strike the margin of the sphenoid wing. Sometimes the holes were made through the coronal suture and the instruments angled backwards reaching the base from 6 mm. to 20 mm. behind the sphenoidal wing. In 24 cases the incisions were made 1 cm. behind the coronal suture and aimed parallel with the suture. In all these cases the white matter was cut through to the base as well as both medially and laterally.

Transorbital lobotomy was carried out with a special leucotome, a pointed steel shaft about 13 cm. long, that was inserted beneath the eyelid 3 cm. from the midline, aimed parallel with the bony ridge of the nose and driven to a depth of 5 cm. from the margin of the upper eyelid. The handle of the instrument was then carried outward to the bony confines of the orbit. It was next returned half way to the parasagittal plane and driven 2 cm. deeper. The handle of the instrument was then pushed 20 degrees toward the nose and 20 to 30 degrees outward. This completed the simple transorbital lobotomy. In the medium operation, the handle was elevated about 30 to 40 degrees in order to perform a partial oblique sagittal section of the thalamofrontal radiation as it curves around the anterior horn of the lateral ventricle. The deep frontal cut was a continuation of the same to an angle of 45 degrees or more with the plane of the nose. Since the area of cortical damage was small, and far away from the motor cortex, the incidence of seizures was quite low.

Another sidelight concerning the difference between prefrontal and transorbital lobotomy is shown by the incidence of epilepsy when transorbital lobotomy is followed by prefrontal lobotomy or some other operation for the relief of mental disorder. Forty-six patients were subjected to a secondary operation of whom 28 had convulsions. Thirteen of these had their operations elsewhere, nine of them being transorbital lobotomies followed by prefrontal operations. One transorbital lobotomy was followed by topectomy and another by cortical undercutting.

SEVERITY OF CONVULSIONS

An attempt was made to classify convulsions according to their time of onset, frequency, duration and control, but such parcellation yielded little valid information, particularly with such additional factors as medication, reoperation, and dropping out of the study due to death or removal from adequate observation. The convulsions were always generalized, practically always with no aura, and frequently severe and accompanied by incontinence. Sometimes the attacks occurred in series. Four deaths in status epilepticus were recorded. Deaths also occurred from accidents during convulsions, one by drowning, one by scalding (an epileptic operated upon by the transorbital route for a paranoid psychosis) and one probably by the occurrence of an attack while driving his car. The convulsions were only partly controlled by medication, but they tended in nearly half of the cases to subside with the

TABLE 8
SEVERITY OF POSTOPERATIVE EPILEPSY

Convulsions:	*Prefrontal Lobotomy*		*Transorbital Lobotomy*	
	Number	*Per cent*	*Number*	*Per cent*
Rare	49	43	3	60
Infrequent	20	18	1	20
Frequent	45	39	1	20
Total	114	100	5	100

Organic brain disease and operative complications omitted.

passage of years. That the convulsive tendency is still present, however, is indicated by one patient who had several convulsions in the two years following operation, was free for ten years, and then, following a period of stress, suffered a single episode. He has suffered a few minor seizures in the past three years. Other patients have been free from postoperative seizures for ten or more years. One of these patients was of particular interest and was reported in the Freeman-Watts monograph, because there were available electroencephalograms before lobotomy, after lobotomy, and before seizures and after the seizures had come under control. We were indebted to Dr. Herbert Jasper for these tracings.

In order to simplify the tabulations, postoperative seizures have been listed as rare, infrequent and frequent. Their incidence is shown in table 8. Because of the small number of cases in the transorbital series, the difference between the two groups, as regards severity, is not significant. These figures for prefrontal lobotomy, however, are close to those for traumatic epilepsy as reported by Watson.[2]

TABLE 9
INCIDENCE OF POSTLOBOTOMY EPILEPSY IN SEVERAL MENTAL DISORDERS

	Diagnosis	*With Convulsions*	
Schizophrenia:	*Total number*	*Number*	*Per cent*
Hebephrenic	95	33	35
Catatonic	117	43	37
Paranoid	83	18	23
Other	17	2	12
Involutional psychoses	126	23	18
Obsessive states	81	22	27
	519	141	

Preoperative epilepsy, organic brain disease, and operative complications omitted. Prefrontal lobotomy only.

INCIDENCE OF SEIZURES IN VARIOUS MENTAL DISORDERS AFTER PREFRONTAL LOBOTOMY

There appears to be no good reason why one functional mental disorder should predispose to postoperative convulsions more than another. This

was tested, however, and the results are given in table 9. Aside from a somewhat lower incidence of seizures in patients with involutional psychoses there is no significant difference. This brings up the question of age as a factor in the development of postlobotomy seizures, since the immature brain has a greater tendency to respond with seizures to various traumas.

TABLE 10
EFFECT OF AGE UPON INCIDENCE OF CONVULSIONS AFTER LOBOTOMY

Age of Lobotomy	*Prefrontal*			*Transorbital*		
	Total Cases	*With Convulsions*		*Total Cases*	*With Convulsions*	
		No.	*%*		*No.*	*%*
Under 21	16	3	19	12	1	8
21 - 40	304	62	21	212	2	1
41 - 60	119	19	16	146	3	2
Over 60	40	3	8	24	1	4
Total	479	87		394	7	

Preoperative epilepsy, organic brain disease and operative complications omitted.

EFFECT OF AGE AND SEX ON INCIDENCE OF POSTLOBOTOMY SEIZURES

As shown in table 10, there is some evidence that greater age protects the patient from the chance of postlobotomy convulsions.

On the other hand, as shown in table 11, the preponderance of postlobotomy epilepsy in males is significant. This also agrees with findings in post-traumatic epilepsy in general, and may explain the high incidence of postlobotomy epilepsy in Veterans Hospital, such as that reported by Drubin.[9]

TABLE 11
INFLUENCE OF SEX UPON INCIDENCE OF POSTLOBOTOMY EPILEPSY

	Prefrontal			*Transorbital*		
	Total Cases	*With Convulsions*		*Total Cases*	*With Convulsions*	
		No.	*%*		*No.*	*%*
Male	157	50	31	99	5	5
Female	322	64	20	295	2	1
Total	479	114		394	7	

Preoperative epilepsy, organic brain disease and operative complications omitted.

RELATION OF POSTLOBOTOMY SEIZURES TO SOCIAL ADJUSTMENT TWO YEARS AFTER LOBOTOMY

The total number of patients in this study that have been followed to the period of stabilization is 1020. This means that 100 of the original patients operated upon have been dropped from the study because of death, inadequate information, or disability due primarily to painful conditions, and a few cases that did not seem to fit anywhere. Conclusions drawn from the material in regard to social adjustment are permissible with some reservations.

TABLE 12

RELATION OF CONVULSIONS AFTER LOBOTOMY TO LEVEL OF SOCIAL ACHIEVEMENT

	Prefrontal				*Transorbital*			
	Good status		*Poor status*		*Good status*		*Poor status*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Convulsions	43	29	107	71	4	31	9	69
No convulsions	182	43	240	57	214	47	220	53
Total	225		347		218		229	

One factor is age, bringing in its wake disability and retirement not related to the lobotomy. By the end of two years the condition of the patient was usually stabilized. Preferably, in dealing with large numbers, it might be said that those who improve after two years are about balanced by those who decline after that period. In the case of transorbital lobotomy the one year period was taken, both because of the smaller numbers under prolonged observation and because of the more rapid stabilization of the psychotic or neurotic patient after the minor operation. The results are shown in table 12. By good social achievement is meant regular or partial employment, keeping house, attending school and generally self-supporting. Poor status includes all hospitalized patients, whether employed or not, as well as patients who are cared for at home by the family or by others, but who are not able to maintain themselves without assistance. The figures are suggestive of a higher incidence of seizures in those with a poor level of social achievement. One possible explanation is the more diligent recording of convulsions by hospital personnel. Another is the greater incidence among those with poor social achievement of radical lobotomy for the relief of violent behavior. Only rarely do the convulsions of themselves prevent a patient otherwise qualified from undertaking some useful occupation. The number of cases in the transorbital series is too small to be significant.

Stevens and Mosovich[10] in the first comprehensive electroencephalographic study of lobotomy patients found abnormal tracings in the frontal regions in all but one of 24 cases, although seizures occurred in only ten. They considered that 21 of 23 patients benefited from operation, and nine were able to leave St. Elizabeth's Hospital. These patients are included in the Freeman and Watts series.

RELATION OF POSTLOBOTOMY SEIZURES WITH DEGREE OF INCAPACITY BEFORE OPERATION

The above tabulation is quite different from that presenting itself in a study of patients previous to operation. The results of this investigation are given in table 13. Patients with mild to moderate incapacity were those able to live at home and take part in some useful activities although they were hampered by their emotional distress. Those who were dependent were able

to live at home, but could contribute nothing to the home environment. The others were hospitalized, including a large number of violent patients who required almost constant seclusion. There is no apparent relationship between the degree of disability or incapacity and the occurrence of postlobotomy seizures. The high figures in the mildly incapacitated and the "hospitalized, quiet" are based on too small numbers to be of much significance. Tabulations of the duration of disability before lobotomy also showed no significant relationship to the incidence of postlobotomy convulsions.

Most of the conclusions that are arrived at from a study of the data correspond well with those derived from experience with post-traumatic epilepsy in general. Convulsions are more common in men than in women, they are more common when lesions approach the motor centers. Outstanding is the influence of cortical trauma as shown by multiple operations and by patients surviving operative complications. The most important feature in this study is the greater freedom from postlobotomy epilepsy of those undergoing transorbital lobotomy.

TABLE 13
RELATION OF POSTLOBOTOMY CONVULSIONS TO DEGREE OF INCAPACITY BEFORE OPERATION

Degree of Incapacity	*Prefrontal*			*Transorbital*		
	Total Cases	*With Convulsions*		*Total Cases*	*With Convulsions*	
		No.	*%*		*No.*	*%*
Mild	9	5	55	17	0	0
Moderate	73	10	14	66	1	2
Home, dependent	130	23	18	81	3	4
Hospital, working	23	7	28	22	0	0
Hospital, vegetating	34	14	42	47	0	0
Hospital, violent	210	55	25	161	3	2
	479	114		394	7	

Preoperative epilepsy, organic brain disease, and operative complications omitted.

LOBOTOMY IN EPILEPTICS

A surprising finding in this study was the reduction of convulsions in some patients previously subject to seizures. This has been noted by a few authors. The most extensive report comes from Brazil where Barretto[11] studied 100 epileptic patients after prefrontal lobotomy. Excluding six patients with insufficient observation, the author found that 13 patients had fewer seizures and 18 had fewer seizures and also relief of concomitant mental symptoms. Only one patient had seizures more frequently. The operations were based on the observation of asymmetry of the brain, lateralization of seizures either spontaneous or provoked by Metrazol and upon pneumoencephalographic

findings. There were no electroencephalographic studies. "These verifications suggested the possibility of correcting the predominance of the major hemisphere by surgery." Patients were operated upon first on one side (usually the left) and later on the opposite side, sometimes both sides at the same time. Six patients did well with left sided operations, seven with right sided operations, six when the right side was sectioned after the left, one when the reverse order was done, and nine when both sides were operated upon at the same time. Only 33 of the patients were observed for more than one year, but about half of the favorable results were found in this group. A further report on these cases is highly desirable, especially since Yahn[12] as early as 1946 came to the conclusion that: "Leucotomy cannot be, for a while, used as a routine method of treatment for epilepsy." One of his patients, however, made a full recovery both from seizures and from the attending personality difficulties. Better results are reported by the same author following temporal lobotomy.[13]

Sometimes the effects of prefrontal lobotomy on epileptics are truly remarkable. Fiamberti and Cameroni[14] observed a patient with complete freedom from convulsions for eight years after transorbital lobotomy. Beaudouin's case,[15] reported only by title, greatly impressed Feuillet.[5] Feuillet, Collin, Thiebaux and Thiebaux[5] studied the question of epilepsy and prefrontal lobotomy in 150 cases. Their convulsive rate after one year was 12 per cent. "If prefrontal lobotomy can produce epilepsy in certain subjects," they state, "it may also at times ameliorate a pre-existing convulsive disorder." This is not uncommon, although usually transitory; "but lasting suppression, even if incomplete, is not impossible." They include the report of a 53 year old woman with frequent seizures followed by confusion, violence, soiling and tearing. Thirty months after lobotomy she was relieved of both the attacks and the supposed deterioration. Boittelle et al.[16] observed 12 epileptics for one to two years after lobotomy was performed for behavior disturbances associated with this disease and were pleased to note that not only were the behavioral changes altered for the better so that six of the patients could live at home, but also that the convulsions occurred less frequently.

There are no striking instances of relief of convulsive states among the patients in this study (see appendix). Some patients had convulsions during infancy, but not since then. Two had spontaneous convulsions following shock therapy, but these cleared up and were not evoked by lobotomy. Two or three of the patients may have had convulsions as isolated phenomena in states of extreme emotional tension, convulsions that may have been hysterical in nature. Lobotomy in five epileptics with psychosis saw suppression of convulsions for a period ranging from a few months to two years, but the convulsions then returned. There are, however, three patients in whom there is no doubt about the relief of convulsive seizures that had recurred with moderate frequency before lobotomy and that ceased thereafter for periods ranging from three to eight years.

There are three possible explanations why patients with preoperative seizures lose this tendency. Granting that observation and time relationships are important, there is a distinct possibility that lobotomy may sever the connections of an epileptogenic focus in the frontal lobe not discernible by electroencephalography. There is also the possibility, more likely than the first, that the general quieting of the emotional pattern may make for better balance of the physical and chemical and metabolic patterns that have something to do with the precipitation of seizures. A third possibility is the subsiding effects of preoperative shock therapy that had produced spontaneous convulsions.

CONCLUSIONS

More than a thousand patients followed an average of five years after prefrontal lobotomy and two years after transorbital lobotomy have yielded a total of 171 patients with convulsive seizures after operation. For more adequate analysis of the epileptogenic effects of lobotomy, the patients were trimmed down by excluding those who had previously had epilepsy, and those who suffered from operative complications. There remained 137. Preoperative electroshock therapy was found to be an insignificant factor. It may have been responsible for a few patients who had convulsions before lobotomy but not afterwards.

Operative and postoperative complications increased the incidence of postlobotomy epilepsy. More important still was the performance of multiple prefrontal lobotomies. The surgeon undertaking reoperation is faced with increased hazards in respect to postoperative epilepsy. The worst combination possible is the presence of organic brain disease, operative complications and multiple lobotomies. Here the incidence of seizures rises to 86 per cent in the prefrontal series.

In general, the closer the incisions come to the motor cortical centers, the more likely the patient is to have postoperative epilepsy. In this respect the transorbital operation is safer.

Postlobotomy convulsions can be controlled in about 60 per cent of cases; thus they differ little from other post-traumatic epileptic states. There is no unusual incidence of postlobotomy epilepsy in any of the psychoses. Possibly there is slightly less frequency among the involutional patients. Advancing age lessens the incidence of seizures. After lobotomy men are more likely to have seizures than women. Patients with convulsions have a lower level of social achievement than those who are free, but a fair number, 43 of 150 patients with seizures, are able to maintain themselves in a useful mode of life after lobotomy. Quiet patients are somewhat more apt to have seizures than violent patients.

The only paradox in this study was the finding of 11 patients who had a history of convulsive seizures before operation, but not afterwards. Allowing for errors in observation and too short a period of follow-up, there still remains

the likelihood that a change for the better in the emotional status of the disturbed patient may also bring about a change in the physical, chemical and electrical components in total behavior that may reduce the incidence of seizures. Another paradox is thus added to the many that beset lobotomy.

APPENDIX

CASES IN THIS STUDY REPORTED TO HAVE CONVULSIONS BEFORE LOBOTOMY BUT NOT AFTERWARDS

Case 149.—This was apparently a faulty designation. The patient from childhood was afflicted by tics that were described as "spasms and jerkings." He has never had a convulsion, followed now for over ten years, since his prefrontal lobotomy.

Case 385.—This patient, according to the record, received insulin and electroshock "after which he had quite a number of spontaneous convulsions." These ceased before his prefrontal lobotomy in 1945 and have not recurred.

Case 452.—The record reads: "She has had two spontaneous convulsions since October (1946) possibly as an aftermath of the insulin and electroshock." There have been no convulsions reported since prefrontal lobotomy in January 1947.

**Case 5175.*—This patient's record has been made available by Doctor Archie Crandell, superintendent of Greystone Park State Hospital. Concerning seizures, the report states: "We find that the only seizure this patient has ever experienced occurred at the age of ten years. The attending physician attributed it to 'indigestion'."

Case 5205.—On reviewing this patient's record with her sister who is a graduate nurse it appears that the "convulsions" were of hysterical type and have disappeared since transorbital lobotomy.

Case 5219.—This patient is reported to have had convulsions in early childhood but none since then.

Case 5293.—The patient had convulsions at the age of 22 months but none since then.

Case 5309.—Doctor F. E. Shovlain, superintendent of Western State Hospital, Ft. Steilacoom, Wash., has investigated the record for me and reports as follows: "There is a statement in the history that she had some convulsions as a child. During her stay here at the hospital (1936, 1939, and continuously since May 1942) there was some thought that her temper tantrums and behavior might suggest a petit mal or epileptic furor. However, this was not borne out by electroencephalographic study. The report came back showing no cortical abnormality."

Case 5324.—This patient was a definite epileptic with infrequent seizures that were kept under fairly good control when she would take her medicine. She was operated upon in July 1949 for schizophrenia with marked obsessive ruminations and depersonalization and has had no further seizures since then.

Case 5472.—Had no recorded convulsions previous to transorbital on May 11, 1950. Beginning in November 1950 she had seizures on seven occasions (up to March 1953) as many as 14 occurring in one day.

Reports on Cases 5472 and 5482 were recently received from Doctor Virginia E. Beyer, Springfield State Hospital, Sykesville, Md.

Case 5482.—This patient experienced seizures in the following pattern:

1949 – 23 grand mal, 4 petit mal
1950 (first half) – 1 grand mal, 2 petit mal
1950 – Transorbital lobotomy June 8
1950 (second half) – 30 grand mal, 14 petit mal
1951 – 83 grand mal, 26 petit mal
1952 – 2 grand mal, 0 petit mal
1953 (to March) – 0 grand mal, 0 petit mal

*The prefix 5 indicates transorbital lobotomy.

A further note concerns Case 125, prefrontal lobotomy on April 13, 1942. Her husband reports in March 1953: "Has not had any seizures since 1947. Prior to her operation these seizures came about six months apart. It seemed that after a hard strenuous day for her she would get weak and get one of those seizures. After the operation she has had two seizures, one in 1944 and 1947, and they were gentle compared with the seizures before operation."

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Next, in numerical importance, among the exciting causes of epilepsy are traumatic influences, blows and falls on the head. To these, after the elimination of doubtful instances, 65 cases were due. A third (21 cases) occurred under ten years, rather more than a third (25 cases) between ten and twenty. Males are affected by this cause more than females, the the number being 39 to 26. This is clearly due to the risks of occupation, for in the cases commencing before ten years the females were in excess. Between ten and forty, the male cases in each decennium were rather more than twice the number of the females. Over forty, the only cases were in men.

Hysteroid attacks rarely result from a traumatic cause. They were met with in only 6 cases out of 44 in which the character of the fit could be determined; and in estimating the significance of these, it must be remembered that traumatic causes often involve intense emotional disturbance.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Arteriographic Evidence of Spasm in Cerebral Vascular Disorders

Arthur Ecker, M.D. and Paul A. Riemenschneider, M.D.*

EXCESSIVE spasm of the cerebral arteries causes ischemia of the walls of the blood vessels and of the cerebral tissues. With Aring,[1] we believe that such contraction is the pathogenic mechanism in many disorders of the brain. Previously spasm has been demonstrated[2] in arteriograms of patients with recently ruptured aneurysms of the circle of Willis. However, some investigators doubt that these arteriograms have actually indicated contraction or spasm of the internal carotid artery and its main branches. Accordingly, the present paper presents further examples and discusses the reliability of such data.

HISTORICAL DATA

In 1942 Egas Moniz,[3] the originator of cerebral angiography, presented a case of transitory right hemiparesis and aphasia. There was subsequent angiographic demonstration of a temporary block in the flow through the uppermost portion of the left internal carotid artery. Moniz considered that only a spasm of the carotid siphon and middle cerebral artery could produce these findings. Nevertheless, it is possible his case was one of pseudospasm.[4] In 1942 Barnes and Trueta[5] published angiographic demonstration of experimentally produced spasm of the femoral arteries in rabbits.

In 1945 Ecker[6] reported four patients with an acute disorder of a cerebral hemisphere ascribed to spasm of the internal carotid artery. In three patients, there had been a "near miss" of the artery in the neck by a missile of high velocity; in the fourth, a blunt head inury.

In 1951, several arteriograms of patients with ruptured aneurysm of the circle of Willis were published.[2] Soon after the rupture the adjacent cerebral arteries were contracted. Some weeks or months later, additional arteriograms showed that the arteries were no longer contracted. However, in one case (case 4, figure 5, p. 664[2]) in successive arteriograms made at the same session, there was evidence of rapid change in arterial caliber.

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Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 9, 1953.

METHODS AND MATERIALS

This material has been drawn from about 600 series of cerebral angiograms performed on 500 patients. These patients were being investigated for various organic neurologic diseases. Our technic of performing angiography has been presented in detail elsewhere.[4] The angiograms used for this presentation have come from five cases, two of spontaneous subarachnoid hemorrhage and three of sudden hemiplegia. The age of the patients ranged from 33 to 41 years. Summaries of the case histories follow:

Case 1.—R. C., male, age 34. Known hypertensive with blood pressure about 170/110. Ten days previously, headache and vomiting; spinal fluid bloody. Right carotid angiography (figure 1A) and indirect vertebral angiography performed. One week later, left carotid angiography (figure 1B) was carried out. There was no evidence of aneurysm or other space-occupying lesion. Subsequently, the patient did well for at least two and a half years.

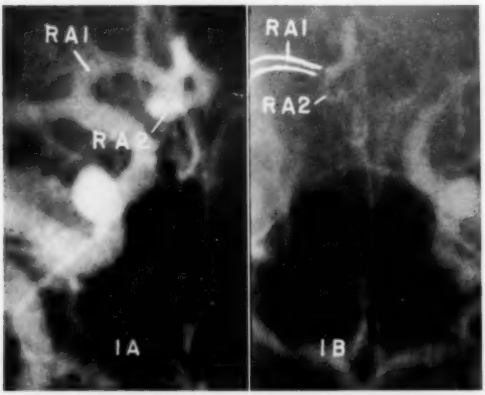

FIG. 1. *Case 1. A.* Occipital view, arteriogram after *right* carotid injection. *B.* Occipital view arteriogram after *left* carotid injection, made one week after 1A. The horizontal portion of the right anterior cerebral artery (RA1) has been retouched. It is much smaller in 1B than in 1A. Likewise the beginning of the ascending portion of the right anterior cerebral (RA2), unretouched, is much smaller in 1B than in 1A. There was no aneurysm in this case.

Case 2.—L. O., male, age 37. Spontaneous subarachnoid hemorrhage with partial left oculomotor palsy June 1950. In May 1951, right and left carotid and vertebral angiography were performed. There was no evidence of any gross vascular aneurysm except a questionable out-pouching on the left internal carotid artery, 1 mm. in diameter. However, the right middle cerebral artery and its main branches showed striking evidence of arterial contractility (figures 2A, B, C). Subsequently, the patient did well for at least 22 months.

Case 3.—T. W., female, age 33. Sudden onset of right hemiparesis and aphasia. Spinal fluid clear and colorless with 110 polymorphonuclear leukocytes per cu. mm., total protein 35 mg. per cent. Left carotid angiography (figure 3A) revealed striking narrowing of the internal carotid artery both in the neck and within the cranium. There was no visualization of the middle cerebral artery. The patient's condition improved. Sixteen months later, repetition of left carotid angiography showed less severe contraction of the left internal carotid and visualization of the middle cerebral artery (figure 3B). Since then the patient has done well for over six years.

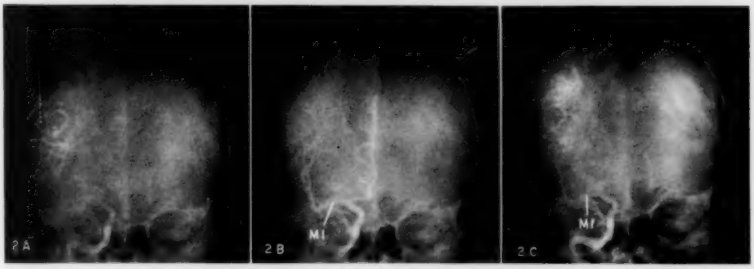

FIG. 2. *Case 2. A, B* and *C* are all occipital views of the arteriograms made after right carotid injection at the same angiographic session. *A* shows pseudospasm; that is, non-visualization of the first portion of the right middle cerebral artery with good visualization of the internal carotid and of the more distal portions of the middle cerebral artery. *B*. Occipital arteriogram after right carotid injection. All arteries (including the first portion of the middle cerebral, M1) appear normal. Compare 2A and 2C. *C*. Marked narrowing of the first portion of the right middle cerebral artery (M1). When compared with 2B it is clear that this is true arterial contraction or spasm.

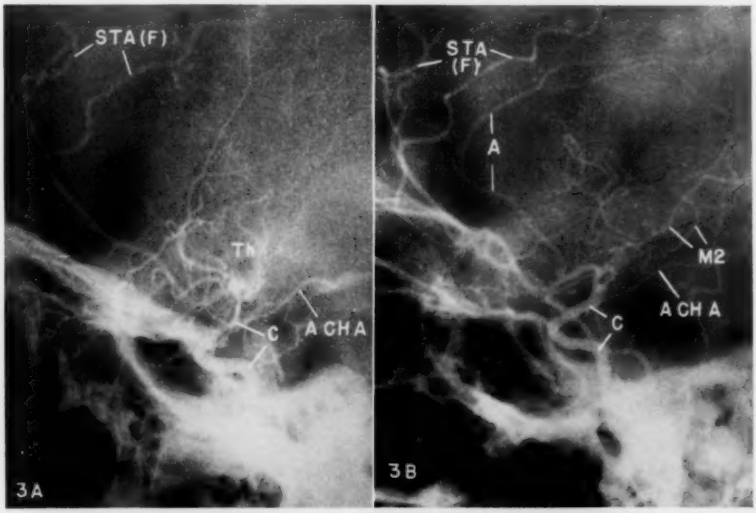

FIG. 3. *Case 3. A*. Lateral view, left carotid arteriogram, 13 days after onset of symptoms. There is striking narrowing of the internal carotid artery, both in the neck and within the cranium (C). There is no visualization of the middle cerebral artery beyond its thalamic branches (Th) or of the anterior cerebral artery. STA (F) is frontal branch of superficial temporal artery. *B*. Lateral view, left carotid arteriogram, 16 months after onset of symptoms. The left internal carotid artery (C) is less severely contracted than in 3A. The middle cerebral artery (M2) is visualized beyond its thalamic branches. The anterior cerebral artery (A) is seen. A CH A is anterior choroidal artery.

Case 4.—H. F., female, age 31. Severe occipital headache for three weeks with recent sudden left hemiparesis. Spinal fluid: total protein 78 mg. per cent, colloidal gold test type D, Wassermann negative. Repetition of spinal fluid study a month later: total pro-

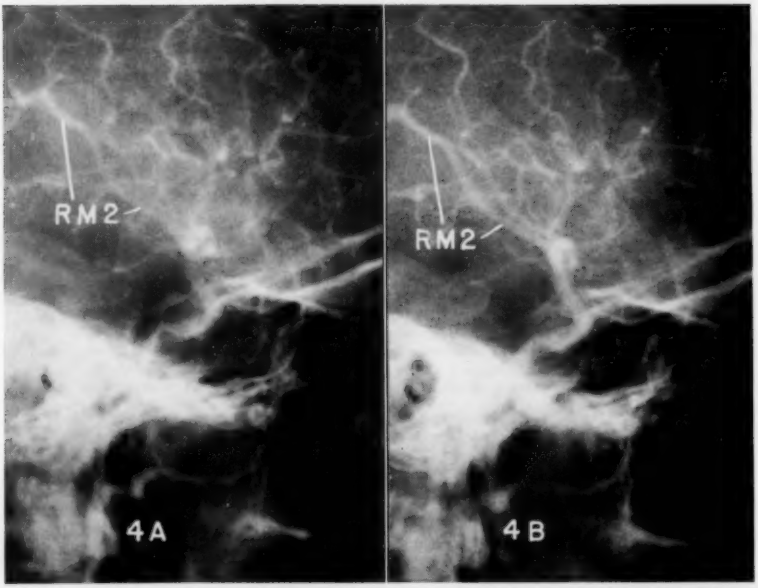

FIG. 4. *Case 4. A.* Lateral view, right carotid arteriogram. The main branches of the right middle cerebral artery (RM_2 and the next vessel anterosuperior and parallel to it) are greatly narrowed. *B.* Lateral view right carotid arteriogram made at the same session as 4A. The main branches of the right middle cerebral are now of normal caliber. Compare with 4A.

tein 95 mg. per cent and colloidal gold test A/B. Right carotid angiography revealed variation in caliber of two major branches of the right middle cerebral artery (figures 4A and B). Subsequently patient's hemiparesis cleared completely. She did well for at least two months.

Case 5.—E. S., male, age 41. Sudden right hemiparesis. Angiography revealed intermittent filling of the internal carotid artery on both right and left sides (figures 5A to D). The patient's clinical condition improved promptly. He remained well for at least two months.

RELIABILITY OF ARTERIOGRAPHIC EVIDENCE OF SPASM IN THE CAROTID ARTERIES AND THEIR MAIN BRANCHES

GRADE 4. *Definite evidence.*

A. Variation of caliber of artery in different arteriograms made with identical technic. The affected length of artery may vary from a few millimeters to several centimeters.

B. Very narrow arteries in arteriogram; normal caliber at autopsy.

C. 3A (as below) and also, later good filling of internal carotid artery and its branches.

GRADE 3. *Excellent evidence.*

A. Good or fair filling of external carotid artery and/or its branches, with no or poor filling of internal carotid and its branches. Exception: Thrombosis of the ipsilateral internal carotid.

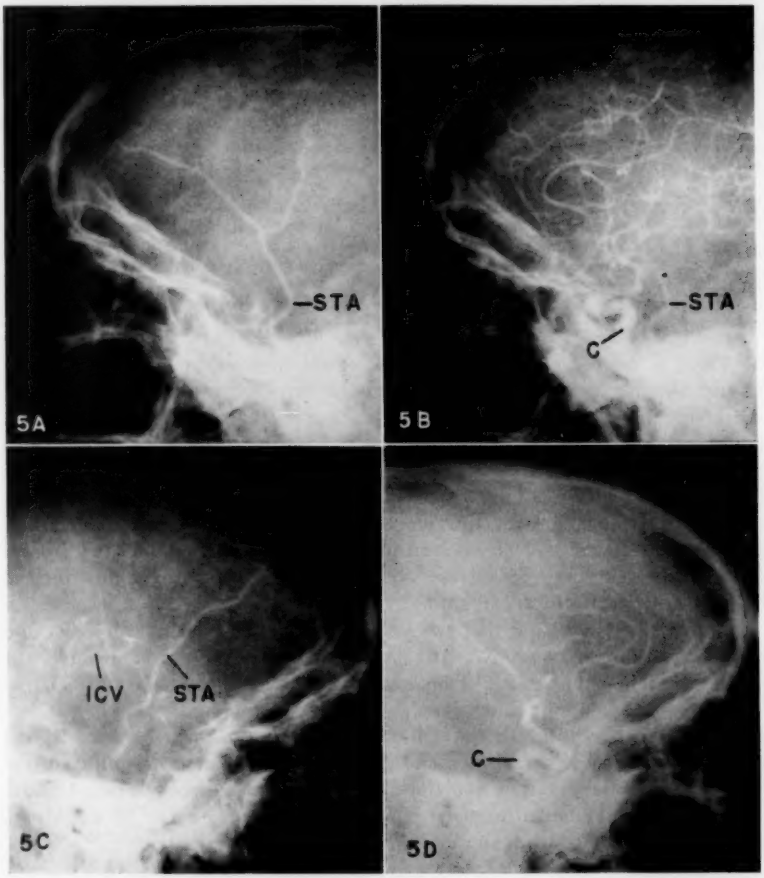

FIG. 5. *Case 3.* A. Lateral view, left carotid arteriogram. The internal carotid artery and its branches are not visualized. Only the superficial temporal artery (STA) and the meningeal arteries, branches of the external carotid, are seen. Compare with 5B. *B.* Lateral view, left carotid arteriogram. The left internal carotid artery (C) and its branches are well seen; that is, the spasm of this artery indicated in 5A has now been relieved. The superficial temporal artery is seen here but not so well as in 5A. *C.* Lateral arteriogram, right carotid injection. The superficial temporal artery (STA) and internal cerebral vein are seen but there is no visualization of the internal carotid artery or its branches. The internal carotid artery and/or its branches are in spasm. Compare with 5D. *D.* The internal carotid artery (C) and its branches are seen well. The branches of the external carotid are not seen.

B. Narrowing of uppermost part of visualized portion of internal carotid artery within cranium (even if no external carotid filled).

GRADE 2. *Moderately reliable evidence.*
- A. Visualization of the contralateral carotid vessels (without use of digital pressure). Exception: Contralateral carotid thrombosis.
- B. Visualization of vertebral-basilar system after injection of right carotid (without digital pressure).
- C. Apparent drawing to a point of the visualized part of the cervical portion of carotid.

GRADE 1. *Slightly reliable evidence.*
- A. Pseudospasm.[4]
- B. No or poor filling of intra- or extracranial arteries in arteriograms, better arterial filling in pictures planned for venograms, that is 5 or 6 seconds later.
- C. General narrowing of severe degree (without either other films showing dilatation or autopsy control). Exception: Obstructive hydrocephalus.

GRADE 0. *No evidence of spasm.*

DISCUSSION

There is smooth muscle in the walls of the arteries, and in the presence of an adequate stimulus, this muscle may be expected to contract. Secondly, surgeons[2,7] have observed variations in caliber of the cerebral arteries at operation. Furthermore, Foltz, Thomas and Ward[8] have seen severe vasospasm of the pial arterioles on inspection of the cortex of animals after intracarotid injection of Diodrast: "This began as a high speed, repetitive series of momentary arteriolar constrictions which gave a fluttering appearance lasting only a few seconds." We have seen a similar effect on the anterior cerebral artery and major branches of the middle cerebral artery in motion picture films* made of carotid arteriograms.[9]

Critics have suggested that what we consider variation in caliber of the cerebral arteries in successive arteriograms may be ascribed to a lamina of blood paralleling the stream of opaque material. This objection fails to recognize that the Diodrast usually replaces the blood completely within the segment of vessel that it fills. Even if the injection were so slow that some blood were alongside the contrast medium at the site of injection, it would not remain as a parallel layer by the time it reached the patient's head. On the contrary, it would be fully mixed. Thus the apparent caliber of the vessel would not be changed but simply its density in the arteriogram.

The question of pseudospasm has been considered in detail elsewhere.[4] Usually it consists of non-opacification of the first portions of the middle and/or anterior cerebral arteries with excellent visibility of both the more distal portions of the affected vessel or vessels and of the termination of the internal carotid artery. Thus the illusion of spasm or pseudospasm is created. It is possible that pseudospasm may have more significance than we have heretofore ascribed to it. The best evidence for this new interpretation is seen in figures 2A, 2B and 2C. Figure 2A demonstrates pseudospasm of the first portion of the middle cerebral artery. Figure 2B illustrates normal arteries; figure 2C shows true spasm of the first portion of the middle cerebral artery. We think that a carotid artery must be hyperreactive if the presence

*These cinefluorographic films were made available to us by Dr. George H. Ramsey.

of a needle in its cervical portion causes enough constriction to produce pseudospasm. No difference has been observed between open exposure of the carotid artery and percutaneous puncture in the incidence of appearance of either pseudospasm or true spasm.

In the presence of good filling of the branches of the external carotid artery, the temporary non-visualization of the intracranial branches of the internal carotid artery is, in our opinion, definite evidence of spasm. The site of the transitory obstruction is usually unknown. It may be anywhere along the course of the internal carotid artery or in its terminal branches. It is useful to compare the two pairs of angiograms in figures 5A-5B and 5C-5D with figures 13A-13B on page 19 of Trueta and co-workers.[10] The latter demonstrate the aortographic effects of the intravenous injection of epinephrine in high dosage. As a result of intense peripheral vasoconstriction, there is non-visualization of the distal aorta, iliac and femoral arteries. But here again the exact site of obstruction remains obscure – whether at these named arteries, their arterioles or even the terminal part of the aorta.

The production of cerebral angiograms is a vasospastic procedure.[8,11] (We have observed transitory aphasia and right hemiparesis caused by the presence of the needle in the wall but not within the lumen of the left common carotid artery.) Therefore, the demonstration of arterial spasm in a given case does not prove that the patient's symptoms necessarily resulted from arterial contraction. (See figures 2C and 5C, which are asymptomatic examples of such spasm.) Conversely, the failure to demonstrate spasm in routine angiograms of a patient does not disprove that his symptoms and signs may have been due to earlier arterial contraction.

Nevertheless, we believe that it is significant that in the general run of angiographic cases, spasm is demonstrable in less than 10 per cent of the cases. On the contrary, in the patients with stroke (including various types of non-traumatic intracranial hemorrhage and cerebral edema or softening) spasm was demonstrable in approximately 90 per cent of the cases. In these patients, therefore, at least the threshold for the production of spasm is lower than normal. It is probable that this situation existed at the time of the ictus and was partly responsible for it. The psychodynamic and pathologic features of arterial contraction and cerebral ischemia are discussed elsewhere.[12]

We are using isolated still photographs to judge a kinetic function. It is a sampling process. For example, it is well known that prolonged contraction of the antrum of the stomach is frequently associated with duodenal ulcer. In the absence of fluoroscopic studies, one might expect in radiographs of the stomach that gastric antral contraction would be demonstrated in about 10 per cent of normals; whereas, such contraction would appear in about 90 per cent of the patients with duodenal ulcer. We believe these well known observations are roughly comparable in significance to that of our data on cerebral arterial spasm. Eventually it is hoped that more will be known about the circumstances under which cerebral arteries contract, especially when studied with motion picture films.

SUMMARY

Arteriographic evidence of spasm consists of visualizing either narrowing of the vessel or abrupt blocking of its flow. When narrowing or blocking is later released, we consider that it had been due to spasm. We have discussed these matters in detail and presented illustrative arteriograms. We have mentioned the probable significance of arterial spasm in the pathogenesis of cerebral stroke.

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Megrim is one of those affections which exhibits the intermittent and paroxysmal characters in a marked degree, and in this respect again maintains a close affinity with the whole family of functional nervous disorders. It is a permanent malady, lasting, in many cases, through the greater part of life, but it is only manifested at more or less distant intervals, in distinct attacks or seizures of a well-defined character and of limited duration, leaving the patient, with few exceptions, in the enjoyment of his usual good health in the intervals. The particular phenomena of the seizure we shall consider in detail by and by; they are directly referrable to the nervous system, and consist for the most part, as we have already sufficiently indicated in the opening chapter, in pain and other disorders of sense, repeating themselves with much regularity on every occasion. We are only here concerned to point out that, as a whole, they exhibit that kind of accession, culmination, and subsidence which essentially belong to our notion of *a paroxysm* or fit of any kind, and the whole attack, in fact, may be not inaptly characterized as a "nerve-storm."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Effect of Intravenous Barbiturates on Abnormal Involuntary Movements

Philip S. Bergman, M.D., Morton Nathanson, M.D. and Morris B. Bender, M.D.

ABNORMAL involuntary movements are classified for the most part symptomatically – that is, by the type of dyskinesia. However, not all involuntary movements which appear similar have the same characteristics under different conditions of investigation. For instance, during sleep some dyskinesias disappear while others persist. Another means of comparing these phenomena is by their response to drugs. The present study concerns the effect of an intravenous barbiturate, sodium Amytal (amobarbital sodium). This drug was used because it has rapid, predictable and easily identifiable effects upon the functions of the central nervous system.

METHOD AND MATERIAL

In-patients and out-patients were studied at Bellevue, Mount Sinai, and Goldwater Memorial hospitals in New York City. These consisted of all the patients encountered in routine clinical material with persistent abnormal involuntary movements.

The following movements were studied: 1) resting tremor; 2) intention tremor; 3) wing-beating movements; 4) hemiballismus; 5) athetoid, choreic, and dystonic movements; 6) myoclonic movements of the palate and other structures; 7) flexor spasms in paraplegia; 8) synkinesias of various types; 9) fasciculations; 10) spontaneous nystagmus; and 11) facial spasms and tics.

The abnormal movements of each patient were examined, and in some cases electrical recordings were made. The recording technique was as follows: Surface skin electrodes were placed on the skin overlying the muscles

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prominently involved in carrying out the abnormal movements, and the resulting combination of electromyogram and movement artifact was amplified and recorded by a conventional electroencephalograph. By using multiple channels, it was possible to compare several participating muscle groups simultaneously. The recordings provided an accurate measurement of rate and rhythm and brought out some relationships which would have been obscure, or at least unconvincing, without them. Eye movements were studied by electrical recording of the corneoretinal potential, as described previously.[1] Synkinetic movements were studied by the usual electromyographic technique, using surface electrodes and implanted coaxial needles. Recordings were made on both the ink-writing and cathode-ray oscillographs. Palatal movements were recorded through the electroencephalograph by means of a stiff, insulated wire with a spherical solder tip inserted just behind the anterior pillar of the fauces.

Each patient was given 2.5 per cent sodium Amytal intravenously at the rate of approximately 50 to 150 mg. per minute, the total dosage depending upon the response of the patient. This dilute solution and slow rate of administration allowed adequate time for observation and recording before and after the patient fell asleep, if that amount of drug was necessary to abolish the movements. Injection of the drug was halted temporarily at the first sign of change in the abnormal movements. During this period the patient was tested for orientation and ability to calculate and carry out commands. In many instances psychic and physical stimuli were introduced and observations were made of their effect on the altered motor activity.

RESULTS

The effect of different amounts of the drug on the various movements is shown in table 1.

TABLE 1

AMOUNTS OF SODIUM AMYTAL REQUIRED TO ABOLISH VARIOUS ABNORMAL MOVEMENTS

Minimal [1]	*Moderate*[2]	*Sleep*	*No Effect*
Parkinsonism	Wing-beating	Choreoathetosis[5]	Myoclonus of palate
Fixation nystagmus	Intention tremor	Flexor spasms[5]	and other structures
	Finger-nose ataxia		
	Hemiballismus		
	Facial spasms and tics		
	Myoclonus[3]		
	Dystonia, including torticollis		
	Synkinesias[4]		

[1]Minimal doses are those which cause just-noticeable side effects (nystagmus, slight euphoria).
[2]Moderate doses cause slow cooperation and some drowsiness, but the patient responds accurately to questions and commands.
[3]Myoclonus referred to here was an isolated instance described fully in the text.
[4]These synkinesias were those in which there was movement of two or more distinct parts when movement of only one was willed. An example is "mirror movements."
[5]These conditions varied widely in response. Usually they disappeared only in sleep.

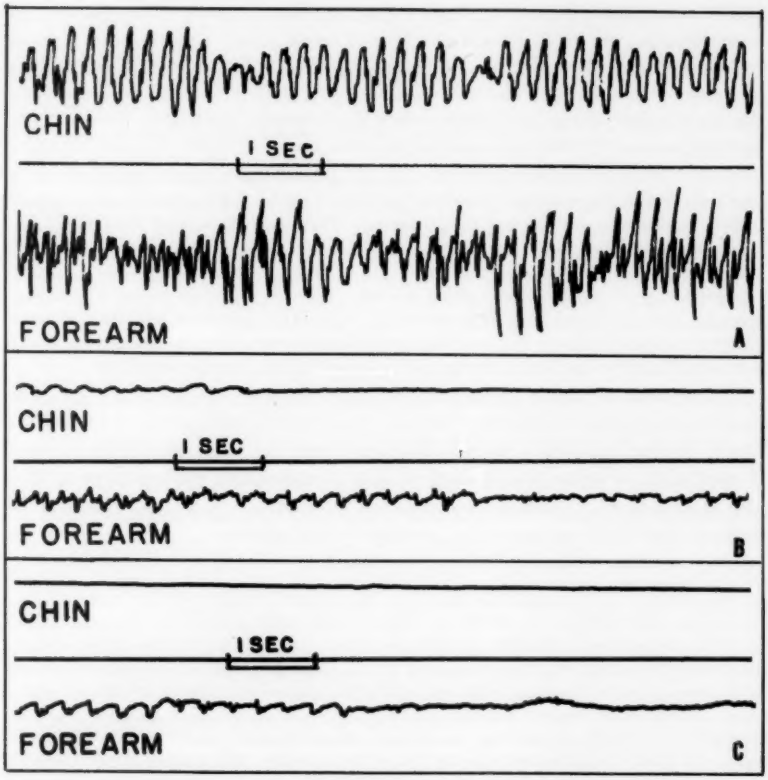

FIG. 1. *Case 1. A.* Before Amytal, chin and forearm tremor are synchronous and regular at 5 per second. *B.* After 40 mg. of sodium Amytal, the chin movement slows and then stops; the forearm movement fluctuates and is slower in rate. *C.* After 75 mg. of sodium Amytal, the forearm tremor becomes slower and stops altogether.

Movements Abolished by Small Amounts of Amytal

The amount varied considerably from individual to individual, but in each case the dose which produced just-noticeable side effects (nystagmus and euphoria) was given.

Resting tremor: The resting tremor became reduced in amplitude, then stopped periodically and later disappeared completely. The hand tremor usually disappeared before that of the leg, if both were present before. The effect was always transient and the tremor began to return within a few minutes. At first it returned briefly if the patient became upset or concentrated on some task (such as calculating) not involving the affected extremity.

Later it fluctuated without obvious cause, increased slowly in amplitude, and then returned to its former state. The accompanying rigidity was reduced by estimation of the resistance to manual manipulation, but it was not possible to detect this difference electromyographically. Other tremors accompanying the movements of the extremities were also stopped, including head, tongue and lip movments, although not all simultaneously.

Case 1.—Paralysis agitans: L. S., 50 years of age, had had tremor of the hands for 24 years, and within the past few years had progressed to the point where he was confined to bed, unable to carry out any useful activity. There was the typical fixed facies, and gross, rhythmic resting tremor of both hands, the lower jaw and tongue, at about 130 per minute (figure 1A). There was marked rigidity of all the extremities.

He was given 2.5 per cent sodium Amytal. After 40 mg. (one minute) nystagmus appeared and the tremor stopped periodically (figure 1B). After 75 mg. (two minutes) all tremor stopped (figure 1C). At this time he answered questions correctly and carried out all commands. Resistance to passive stretch of the muscles was less.

Nystagmus on direct forward gaze: The findings in regard to nystagmus have been reported elsewhere. In brief, congenital or acquired nystagmus on direct forward gaze disappeared following small amounts of sodium Amytal. If oscillopsia or other visual disturbances accompanied the nystagmus, they also disappeared. Nystagmus on lateral or vertical gaze was changed by sodium Amytal in various ways, usually by the addition of new frequencies, accompanied by a complete change in character. The drug produced nystagmus on lateral and vertical gaze if it was not previously present.

Case 2.—Spontaneous nystagmus on direct forward gaze: (multiple sclerosis). W. K., 32 years, complained of blurring of vision for three years. He stated that "print and objects shake from side to side" (oscillopsia). On examination there were horizontal and rotary nystagmus on direct forward and both lateral gazes and vertical nystagmus with a rotary component on upward and downward gaze.

Electrical recordings prior to intravenous sodium Amytal showed regular sinusoidal waves at five per second in both eyes on direct forward gaze, more marked in the "vertical" channels (figure 2A). Nystagmus was recorded also in all other directions of gaze (not illustrated).

One hundred mg. of sodium Amytal was given intravenously in 15 seconds. One minute later the patient reported that the oscillopsia stopped. Five seconds later the record showed that the nystagmus on direct forward gaze also was gone (figure 2B). It was noted, however, that the nystagmus in all other directions became more prominent and changed in rate and character. The nystagmus on forward gaze reappeared eight minutes after completion of the injection, but only in short bursts. The oscillopsia did not return until the nystagmus resumed its previous consistent rate and character, which was about 15 minutes after completion of the injection.

Movements Altered by Moderate Doses

These doses produced drowsiness, slurred speech and slow cooperation, but the subjects responded accurately to commands and questions. The cases below are given for illustrative purposes.

Intention Tremor: The following case illustrates the response of various components of tremor to intravenous Amytal.

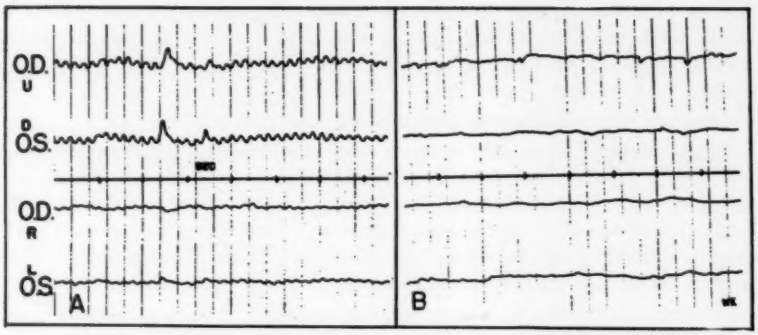

FIG. 2. *Case* 2. Eye movement (corneoretinal potential) recording. The first and second channels record vertical movements in the right and left eyes respectively. The third and fourth channels record horizontal movement in the two eyes.
A. Before Amytal, there are regular sinusoidal waves (pendular nystagmus) at 5 per second, chiefly in the vertical channels of the two eyes. *B*. After Amytal, the record shows only random eye movement of small amplitude. The nystagmus has stopped, corresponding to the disappearance of the sinusoidal waves.

Case 3.—(*Wilson's disease*): C. P., aged 23 years, had had progressively severe shaking of all his extremities and increasing difficulty in using them for four years. On examination he showed a coarse, regular, alternating tremor of the head and extremities at rest. When he held out his hands there were gross flapping movements, particularly at the wrists. When he attempted to touch his nose with his index finger, the tremor was greatly increased and became even more violent when he tried to keep it on the nose. The eyes showed an irregularly periodic, coarse, vertical nystagmus on all directions of gaze, including straight forward gaze. There was bilateral marginal pigmentation, greenish-brown in color, at the posterior surface of the cornea (Kayser-Fleischer rings). The diagnosis was hepatolenticular degeneration.

After receiving 50 mg. of sodium Amytal in 25 seconds, the resting tremor in the right upper extremity stopped completely, and appeared only sporadically in the left upper extremity. The nystagmus was unchanged. Three minutes later after 150 mg. were injected, all resting tremor stopped and the intention tremor was decreased in amplitude. The nystagmus on direct forward gaze stopped and that in all other directions changed to a fast, shimmering nystagmus. As more drug was given (300 mg.) the finger-to-nose dysmetria became progressively less pronounced, and he was able to hold his finger on his nose for longer periods of time. After 500 mg. in 14 minutes, he was able to hold his finger on his nose for as long as 60 seconds. During this maneuver there were slight alternating movements of the fingers being used, but no movement of the larger joints was noted. He was drowsy at this point, but he related accurately and was perfectly oriented.

Other patients with one or more of these tremor components behaved in a similar way.

Dystonia in all its forms was abolished by moderate doses. This includes spasmodic torticollis and various spasmodic movements of the mouth and eyes. The "static" element of dystonia is less easily affected.

The *synkinesias* studied were of two principal types. In one there are "mirror movements" or other involuntary movements of distant parts when some voluntary motor act is performed. These are readily abolished by sodium

Amytal. The second type includes those appearing in the face as residua of facial nerve paralysis. These persist with fairly large amounts of sodium Amytal, but sufficient material has not yet been studied to derive a consistent pattern.

Movements Which Disappear With Sleep Doses

Some movements in this category were abolished by smaller doses, but this varied. In choreoathetosis, for example, certain aspects of the dyskinesia disappear during administration of the drug, whereas other components may not stop except in deep sleep. Flexor spasms in paraplegics disappeared fairly quickly, but they could be elicited by stimulating the lower extremities. With large doses of Amytal they no longer occurred after such stimulation.

Movements Unaffected by Any Amount of Amytal

In this group were all the cases of palatal myoclonus (ten cases) and one case of limb myoclonus. Palatal myoclonus was not affected by doses of Amytal to the point of deep sleep.

Myoclonus is not yet completely understood clinically or pathologically. Clinically similar muscular contractions classified as "myoclonus" may have entirely different responses to intravenous Amytal and may therefore be due to different pathophysiologic mechanisms. The following cases illustrate this problem.

Case 4.—In this case (figure 3) there was continuous myoclonus of the extremities and buttocks. They persisted in sleep, after stupor-producing doses of sodium Amytal, and after spinal anesthesia to the point of complete paralysis of voluntary motion. They could be stopped, however, by curare and reinstituted by a curare antagonist.

Case 5.—This case (figure 4) was characterized by a left cerebral lesion and myoclonus of the extremities and abdomen on the opposite side, identical in appearance to those of the first case. Here there were occasional spikes in the electroencephalogram in variable relation to the muscle twitches. The muscle contractions were abolished by sodium Amytal, but the electroencephalogram was unaffected. When the myoclonus disappeared spontaneously in the course of time, the spikes were replaced by focal slow waves.

Case 6.—Another case in which palatal myoclonus existed with resting tremor of the extremities is illustrated in figure 5. Clinically, it was not clear whether the peripheral tremor was related to the movements of the palate and lips. After Amytal the movement of the extremities stopped, but the palatal movements persisted even in sleep.

COMMENTS

Abnormal involuntary movements were shown to act in a characteristic way following the intravenous administration of sodium Amytal. Some responded to very small amounts, while others were not affected by doses producing stupor. Since only cases of palatal myoclonus and one case of limb myoclonus proved to be completely resistant to Amytal, there may be a common pathologic basis for such movements.

Sodium Amytal given intravenously to normal subjects or to patients with disease of the central nervous system causes the appearance of some involuntary movements. Small doses regularly produce nystagmus on lateral, upward, and sometimes downward, gaze. This is an early and extremely per-

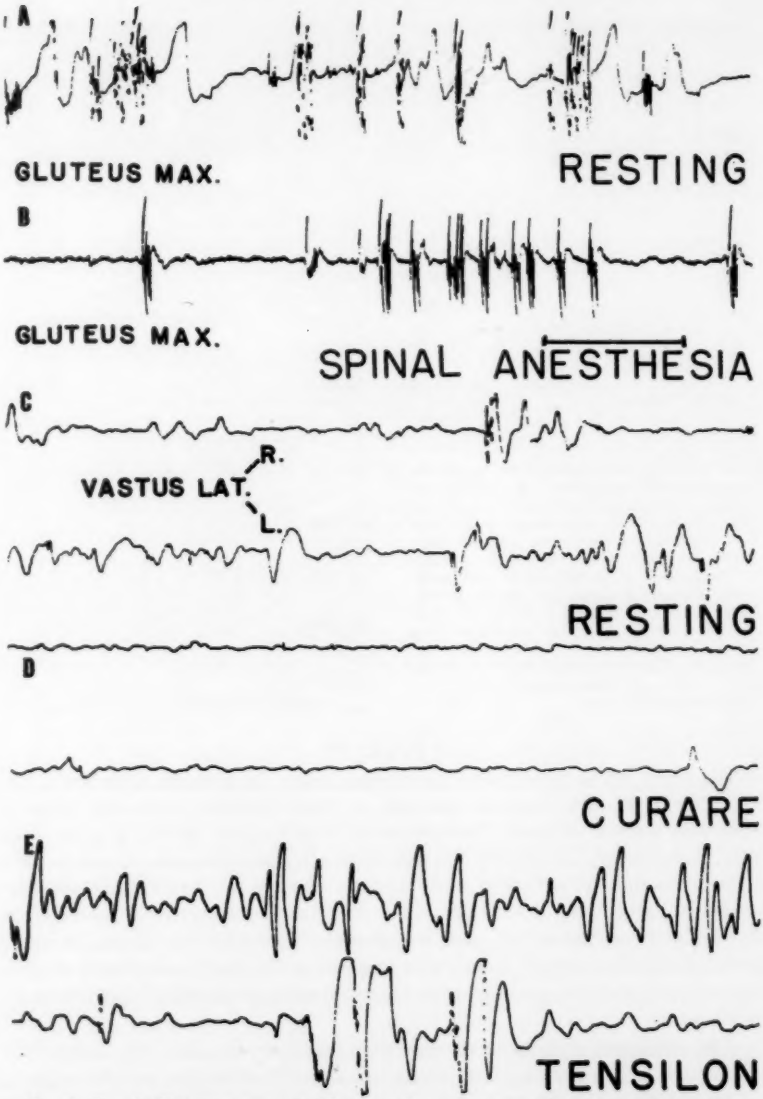

FIG. 3. *Case 4.* Electromyograms. *A.* Gluteus maximus. Spontaneous irregular muscular contractions. *B.* Spinal anesthesia has produced total paralysis below the diaphragm. The previous contractions persist. *C.* Vastus lateralis, right and left. Irregular contractions occur spontaneously. *D.* Curare has produced almost complete paralysis. The spontaneous contractions are almost completely abolished. *E.* Tensilon given after the record in *D* resulted in return of the spontaneous contractions, in augmented form.

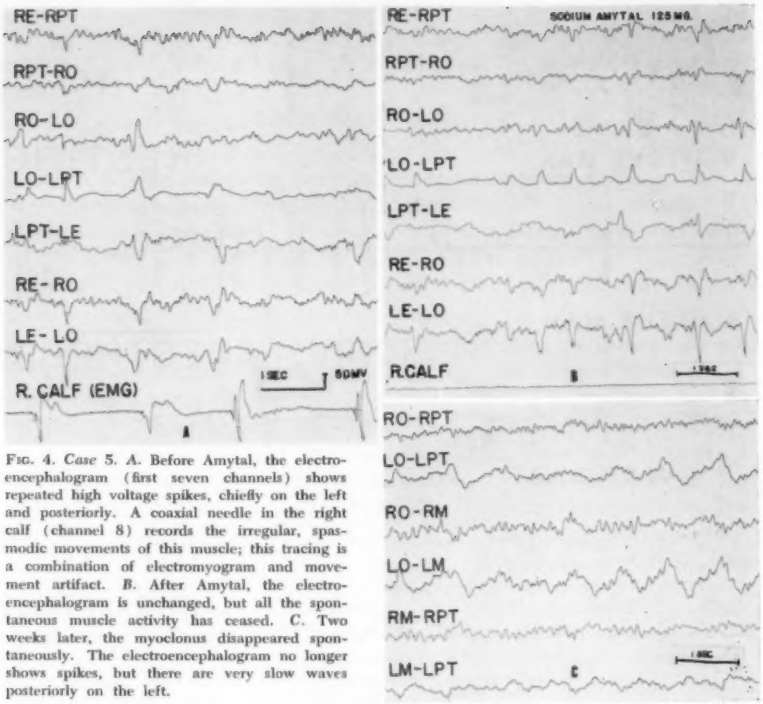

FIG. 4. *Case* 5. *A*. Before Amytal, the electroencephalogram (first seven channels) shows repeated high voltage spikes, chiefly on the left and posteriorly. A coaxial needle in the right calf (channel 8) records the irregular, spasmodic movements of this muscle; this tracing is a combination of electromyogram and movement artifact. *B*. After Amytal, the electroencephalogram is unchanged, but all the spontaneous muscle activity has ceased. *C*. Two weeks later, the myoclonus disappeared spontaneously. The electroencephalogram no longer shows spikes, but there are very slow waves posteriorly on the left.

sistent effect when barbiturates have been taken. In patients with brain disease, the type of nystagmus induced is often different from that seen in otherwise normal subjects. Dysmetria on finger-to-nose testing is often seen after barbiturates. It usually appears only after considerable amounts have been given and the patient is quite drowsy. During the intravenous administration of barbiturate, it has been noted that some subjects exhibit movements of the hands or feet which may be athetotic, myoclonic, or tetanic in character. These also require large doses and are more often encountered in normal subjects than in patients with brain disease or pre-existing involuntary movements.

The abolition of movements was transient in every case, and unless the patient fell asleep the effects rarely lasted more than 15 minutes. Nystagmus on lateral gaze resulting from the injection usually persisted for 20 to 30 minutes.

The rigidity of parkinsonism was not affected to the same extent as the tremor, but the "cogwheel phenomenon" was no longer present on passive

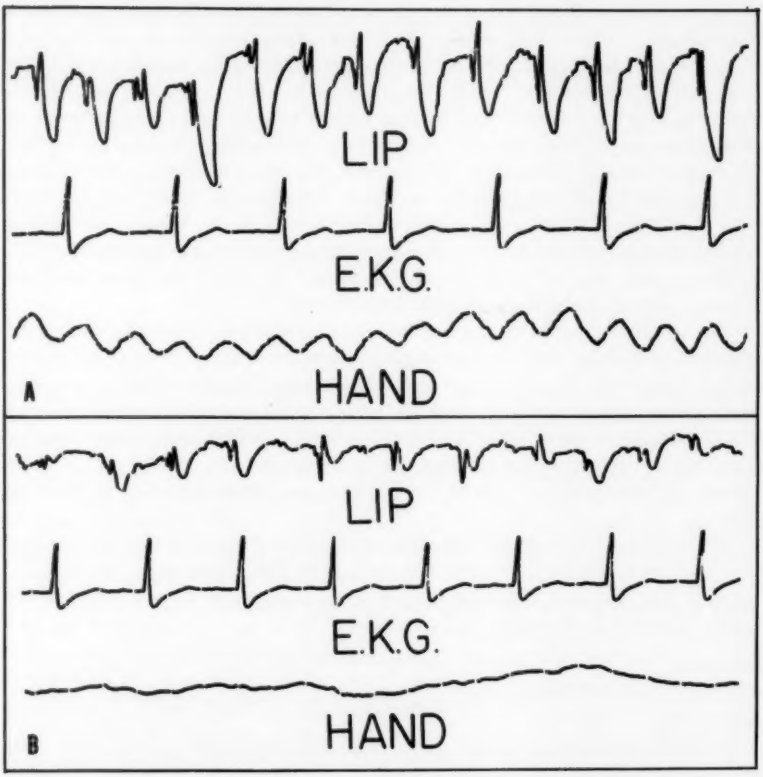

FIG. 5. *Case 6. A.* Before Amytal, the lip movement, hand movement and heart record are regular, but no two are synchronous. The lip movement was synchronous with the palatal myoclonus (not recorded). *B.* After Amytal, the lip movement retains its former rate but is reduced in amplitude. It persisted even in deep sleep. The hand tremor was easily abolished with sodium Amytal.

stretching of the muscle. As the tremor disappeared, there was a reduction in both rate and amplitude. Schwab and Cobb,[2] using recordings, found a constant rate of parkinsonian tremor under various conditions in spite of variations in amplitude.

Rigotti and Stefanini[3] reported reduction or abolition of the movements in several cases of parkinsonism, choreoathetosis and Sydenham's chorea by the use of sodium Pentothal intravenously. Their findings are essentially in agreement with ours, although the rapid action of Pentothal does not permit detailed observation of the stages in the disappearance and reappearance of the abnormal movements.

Others have studied the effect of various drugs on abnormal involuntary movements.[4,5] Garai[6] temporarily abolished parkinsonian tremor and reduced rigidity by means of amyl nitrite inhalations. Stephen and Chandy[7] and Gammon and Churchill,[8] using Mephenesin in doses sufficient to produce nystagmus, slurred speech and loss of ability to converge, demonstrated reduction or abolition of the movements in parkinsonism, choreoathetosis and hepatolenticular degeneration. In addition, the rigidity of parkinsonism and of congenital spastic diplegia was reduced. Chorea was unaffected, probably because the doses given were insufficient to induce sleep. These observations, combined with the work of the authors and others on the effects of Mephenesin on the eye movements[1,9] and other phenomena,[10] point out the great similarity of action between Mephenesin and the barbiturates.

The intravenous injection of barbiturates has often been used to distinguish apparent neurologic signs of psychogenic origin from those of organic disease, on the theory that the relaxation and other mental changes which occur after barbiturates will cause the disappearance of psychogenic phenomena, whereas organically determined signs will be unaffected. These and other observations clearly indicate that intravenous barbiturates may induce a profound change in neurologic manifestations which are unquestionably organic in origin.

Although only two of our patients had unilateral cerebral disease, the fact that a hemiparesis became apparent only after the movements had stopped suggests that the use of intravenous barbiturates under these circumstances might have some diagnostic value.

SUMMARY

1. The effect of intravenous barbiturates in a variety of abnormal involuntary movements was investigated.

2. It was possible to classify these abnormal movements according to their response to intravenous sodium Amytal.

3. The abolition of many of these movements showed a characteristic pattern.

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A Parenchymatous Cerebellar Syndrome Following Protracted High Body Temperature

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CEREBELLAR DYSFUNCTION beginning in adult life, in individuals with neither surgical lesions nor personal or familial history of other neurologic disease, has been reported from time to time. Parker and Kernohan,[1] in a review of the literature up to 1933 were able to add 13 such cases to one of their own. The typical clinical picture is one of ataxia and dysarthria of gradually progressive nature with little or nothing in the way of other neurologic findings. Characteristically this is a syndrome of late life. In those cases which come to autopsy there is loss of the Purkinje cells.

In 1940 Romano, Michael, and Merritt[2] differentiated a syndrome similar in its clinical manifestations to that of Parker and Kernohan but distinguished by a pre-morbid history of excessive alcoholic intake.

Still a third group of cases characterized like the foregoing by a cerebellar syndrome beginning in adult life, but distinguished from them in its abrupt onset and non-progressive course, has been noted occasionally. Five such cases have been reported in the English literature since 1912. Each has been characterized by an episode of hyperpyrexia followed by the development of ataxia and dysarthria with few or no signs of involvement of other elements of the neuraxis. The origin of the hyperpyrexia has varied from case to case. Weisenberg's[3] patient (case 1 in his paper) suffered a sun-stroke as did those of Stewart[4] and Freeman and Dumoff.[5] Cruickshank's[6] patient developed hyperpyrexia with rectal temperatures ranging up to 110° F. in the course of acute rheumatic fever. Following a subtotal thyroidectomy rectal temperatures as high as 108.4 F. were recorded in Silverman and Wilson's patient.[7]

The following new cases are reported as further instances of this syndrome.

CASE REPORTS

Case 1.—A 51 year old ship's engineer was referred because of marked ataxia and dysarthria of eight months' duration. At the time in good health, he was assigned on the

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morning of June 23, 1951, to repair the port boiler of his ship. The heat was so intense that a wooden boardwalk had to be constructed on the already insulated boiler top. After working continuously in this environment from 8 a.m. to 3 p.m., he had to move away because his legs were weak and would not function. His last recollection was of taking over manipulation of the ship's power plant about one hour later.

A series of radiograms from his ship read as follows:

"1. Man aged 51 ass't engineer suddenly seized with violent trembling in engine room. Mutters constantly, mostly unintelligibly, remainder meaningless. Very hot skin. Unable to take temperature, unaware of surroundings."

"2. (1 hour later) Patient unconscious, Resp. 40, Pulse 102, Temp. 105.5, Skin hot and dry."

"3. Unconscious, eyes open, shaking, continuous 1 hour, skin hot and dry, violent diarrhea."

Examination on admission to a local hospital on the following day revealed a comatose but well developed and nourished man. Temperature on admission was 103.6 F., pulse 112, respiration 32, blood pressure 130/82. The neck was stiff. Muscle tone was increased throughout. The tendon reflexes were slightly increased on the right and the right plantar response was equivocal. The muscles of the right upper and lower extremities twitched continuously. The skin was hot and dry and showed decreased turgor. The liver margin was one finger's breadth below the right costal margin. A lumbar puncture done the day after admission showed grossly bloody fluid under normal pressure. Repeated urinalyses revealed marked albuminuria, numerous red and white cells, and hyaline and granular casts. The red blood cell count was 3,850,000 per cu. mm.; white count 5,500 per cu. mm., with 73 per cent polymorphonuclears, 25 per cent lymphocytes and 2 per cent monocytes. Bleeding time was 3′ 30″, coagulation time 1′ 30″ Platelet count was 119,350. Prothrombin time was 20 per cent of normal. The blood serum was deeply icteric. Serum nonprotein nitrogen was 27.9 and CO_2 combining power 36 volumes per cent. Serology was negative both in the blood and spinal fluid. Stool and blood cultures were negative. Agglutinations for typhoid, O and H, paratyphoid A and B, proteus OX–19 and B. Abortus showed no significant titers.

The patient remained comatose for the first four hospital days. During this period his rectal temperature fluctuated between 103 and 106° F. The enlargement of the liver noted on admission increased to three finger's breadth and he became icteric.

The coma began to lighten on the fifth hospital day and on the tenth day all evidence of confusion had disappeared. Clinical and laboratory evidence of renal and hepatic disease gradually disappeared during the next two months.

From the time the patient was able to communicate and move it was noted that he was markedly dysarthric and ataxic.

When first seen by the authors on January 22, 1952, he walked with a broad-based shuffling gait. There was marked ataxia of all extremities, unaffected by opening or closing the eyes. Skilled movements were executed poorly. Speech was slurred to the point of being nearly unintelligible. Both horizontal and vertical nystagmus were present. Tendon reflexes were brisk but symmetrical, and plantar responses were flexor. Sensory examination revealed no abnormalities. There was some difficulty in naming objects and some retrograde amnesia.

Re-examination eight months later, on October 30, 1952, revealed a stiff-legged shuffling marché a petit pas. Coordination of arm and leg movements was poor. There was marked slurring of speech. Finger to nose and heel to knee ataxia was still present, as was discoordination on execution of skilled acts. At this time the left side was distinctly more involved than the right. The previously noted changes in the sphere of higher mental functions had disappeared. The patient had, however, developed a delusional system in

which he felt that the insurance company was sending people to trap him and that his attorney was partner to this plot.

Case 2.—A woman aged 58 was admitted to the Tulane neurology unit at Charity Hospital, complaining of difficulty in standing, walking and talking. The patient, a registered nurse, was in good health and practicing her profession until May 1925 (25 years prior to admission), when she consulted a physician because of a bladder and kidney infection. A cystoscopic examination was done with no immediate complications. The patient returned to her home on the same day. Two days later she was found on the floor of her bathroom in coma, and was removed to a local hospital. During the next two months temperatures of 105° F. were recorded repeatedly. Her state of consciousness alternated between coma and semi-lucidity. Upon recovery of consciousness she was noted to be anarthric and immobile. While there was gradual improvement over the next three years, marked dysarthria and ataxia especially in the lower extremities persisted. Examination on August 20, 1950, showed severe ataxia of all four extremities as well as the trunk. The patient could neither stand nor walk unassisted. Speech was thick and scanning to the point of being nearly unintelligible. There was past pointing to the right; check and rebound were poor bilaterally. Slight horizontal nystagmus was noted on extreme lateral gaze to either side. Otherwise the cranial nerves were normal. Tendon reflexes were symmetrical and within normal limits; abdominal reflexes were present and active. The right plantar response was flexor, the left equivocal according to some examiners and definitely flexor according to others. An electroencephalogram revealed generalized random spikes against a moderately fast background. Audiometric examination showed a conduction-type hearing deficit with approximately 30 decibel loss to the left. The remainder of the laboratory data including hemogram, urinalysis, serology, spinal fluid studies, and caloric examination were within normal limits.

On re-examination six months later there was no change in the clinical picture.

DISCUSSION

Despite the fact that Cruickshank[6] states that cerebellar dysfunction following heat stroke is well known, such standard authorities as Brain,[8] Ford,[9] and Grinker and Bucy[10] make no mention of such a syndrome. Wilson[11] mentions ataxia as one of a long series of possible sequelae of heat stroke. Malamud, Haymaker and Custer[12] reviewed the clinical and pathologic features of 125 fatal cases of heat stroke. It is their conclusion that, "changes in the cerebellum were more striking, more consistent, and more rapid in development than in any other part of the brain." Marked reduction in the number of Purkinje cells as well as swelling pyknosis or disintegration of the remaining cells was observed in cases in which death occurred in less than 24 hours after the onset of the clinical syndrome. Where survival was more than 24 hours, destruction of the Purkinje cells was almost complete. Except in cases of several days' duration the molecular and granular layers as well as the subcortical nuclei showed only glial proliferation. The observations of Freeman and Dumoff[5] are in agreement with those of these authors.

Other changes in the nervous system reported by Malamud et al[12] include edema of the brain, patchy congestion, and petechial hemorrhages particularly in the walls of the third, and floor of the fourth ventricle. Degenerative changes in cerebral cortical nerve cells, with alterations of the cyto-architectural pattern and gliosis were observed. Subcortical structures were similarly but less markedly affected than the cortex. It is the conclusion of the authors

that the irreversible damage to the nervous system seen in their cases provides an adequate basis for the cerebellar and mental changes reported in nonfatal heat stroke.

The question is raised by Malamud et al as to the specificity of the sun in the precipitation of heat-stroke. They point out that sunlight is capable of only limited penetration into the body and has no direct effect on the brain and meninges. Rather it would appear from the experiments of Aron,[13] which they cite, that heat-stroke occurs when the whole body is exposed, indicating the precipitating cause of the stroke is the total heat load. It follows that such an increased "heat load" might be of endogenous origin as well as exogenously derived. This would apply in the cases of Cruickshank, Silverman and Wilson, and the present case 2.

SUMMARY

A cerebellar syndrome having its onset abruptly in adult life following a period of hyperpyrexia has been reported from time to time.

Two cases are reported in which such a sequence of events was observed.

Pathologic evidence indicating the selective sensitivity of the Purkinje cells to high temperature is cited.

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Subarachnoid Haemorrhage of Unusual Aetiology

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SUBARACHNOID HAEMORRHAGE is not a disease entity, since it can be produced by a variety of pathologic lesions. Indeed, if all cases are considered in which blood appears in the subarachnoid space, Courville[1] has shown that more than half are due to external trauma, whereas many others occur in the neonatal period or else as a result of extension to the ventricular system of a parenchymatous cerebral haemorrhage. Exclusion of such cases will leave a group of patients in which the distinctive clinical picture of "spontaneous subarachnoid haemorrhage" will be recognized. The work of Symonds[2] suggested that this syndrome usually results from rupture of an aneurysm of one of the arteries of the circle of Willis or its branches, and this opinion has been amply confirmed, although it is now clear that an identical picture may sometimes be produced by the rupture of a previously asymptomatic cerebral angioma. However, although aneurysmal or angiomal rupture undoubtedly accounts for the majority of cases, from time to time numerous other pathologic conditions may underlie a brisk attack of subarachnoid bleeding.

Sometimes the primary lesion will have produced symptoms or signs beforehand, but on other occasions the haemorrhage may be the presenting feature; in such cases recognition of the aetiologic lesion is important from the standpoint of therapy. It is hoped that, by reporting a series of cases of spontaneous subarachnoid haemorrhage of unusual aetiology, attention will be drawn to this small, largely neglected, yet important group of cases.

MATERIAL

The author has described elsewhere[3] the results of a survey of 312 consecutive cases of spontaneous subarachnoid haemorrhage admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, during the years 1940 to 1949 inclusive. The diagnosis was made by the physician in charge of the individual cases and it is assumed that, as far as possible, neonatal cases and those resulting from trauma or primary cerebral haemorrhage were excluded.

Unfortunately, cerebral angiography was not in use in the hospital during the period of the survey and for this reason the aetiology of the illness was not revealed in a large number of patients. It was, however, confirmed that aneurysms were responsible in at least 65 cases, angiomas in a further five;

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TABLE 1

THE AETIOLOGY OF SPONTANEOUS SUBARACHNOID HAEMORRHAGE

INTRACRANIAL ORIGIN	
The main aetiologic lesions	*Subgroups and examples*
1. Intracranial aneurysms	(a) Congenital (b) Mycotic (c) Atherosclerotic
2. Arteriovenous angioma	
3. Other vascular malformations	Haemangioblastoma[4] Telangiectases[9] Sturge-Weber syndrome[10]
4. Arterial rupture without aneurysmal formation	Atheroma[12,13,14] ? Normal arteries[13,15]
5. Intracranial neoplasms	Glioma[21,22,23,24,25,26] Meningioma[20] Metastases of bronchogenic carcinoma[27,29] Malignant melanoma (a) primary[31] (b) secondary[29,32,33,34] Osteochondroma of base of skull[35,36] Pituitary adenoma[37,38,39,40]
6. Blood dyscrasias	Haemophilia[41,42] Pernicious anaemia[43] "Splenic anaemia"[44] Aplastic anaemia[17,51] Leukaemia[17] Agranulocytosis[17] Purpura haemorrhagica[13,17,45,48] Polycythaemia vera[16] Sickle cell anaemia[46,47]
7. Intracranial venous thrombosis	Superior sagittal sinus[17,52,53,54,55] Lateral sinus[56]
8. Inflammatory conditions of brain and meninges	Acute bacterial infections[42,52,53,54] Purulent meningoencephalitis[58] Cerebral abscess[17] Tuberculous meningitis[60,63] Syphilitic meningoencephalitis[64,65] Aspergillus arteritis[67] Relapsing fever[68,69] Infective embolism without aneurysmal formation[75]
9. Focal vascular necrosis[75]	
10. Vascular allergy	Polyarteritis nodosa[80,81,82] Anaphylactoid purpura[84] Haemorrhagic nephritis[17,69,85] *Acute rheumatism[86,87,88]
11. Miscellaneous disorders	*Sunstroke[89] Scurvy and alcoholism[16] Insulin therapy[90,91] Electroplexy[91,92] Pneumoencephalography[17] Metrazol administration[93] *Hodgkin's disease[16]

TABLE 1—(Continued)

SPINAL ORIGIN	
The main aetiologic lesions	*Subgroups and examples*
1. Vascular malformations of the spinal cord and meninges	Arteriovenous angioma[107] Racemose venous malformations[107] Telangiectases[108]
2. Intrathecal neoplasms	Neurofibroma[102,104] Ependymoma[98,101,104]
3. Other causes	Rupture of spinal artery[14]

*It is not yet proven that the relationship of these conditions to subarachnoid haemorrhage is other than fortuitous.

in the 16 cases (5 per cent) to be presented here clinical or pathologic evidence clearly indicated that the bleeding was of unusual origin.

If the diagnostic criteria referred to above are accepted, cases of spontaneous subarachnoid haemorrhage can be classified by aetiology into several distinct groups; a comprehensive classification is attempted in table 1. Table 2 outlines briefly the cases which form the basis of the present study.

Each of the aetiologic agents listed will now be considered in turn, and illustrative cases from table 2 will be described. The cases can be divided into two groups, first those in which the haemorrhage arose intracranially, and a second and much smaller group in which the haemorrhage arose within the theca.

SUBARACHNOID HAEMORRHAGE OF INTRACRANIAL ORIGIN

1. *Vascular malformations other than arteriovenous angiomas.*

The classification of vascular anomalies of the central nervous system is by no means clearcut, but it is well recognized that subarachnoid haemorrhage may arise from the rupture of lesions which are pathologically distinct from the arteriovenous angiomas. Haemangioblastomas which commonly occur in the cerebellum in children may occasionally give rise to subarachnoid bleeding;[4] these structures should probably be classified as neoplasms, but the fact that they are often associated with similar malformations in other organs[5,6] and are frequently familial[7,8] argues a genetic basis. Telangiectasis of the central nervous system may also give rise to subarachnoid haemorrhage[9] and rarely bleeding may occur in cases of the Sturge-Weber syndrome,[10] in which an angiomatous condition of the brain and meninges is associated with a facial naevus. The difficulty of distinguishing between congenital malformations and vascular tumours of the brain has been stressed by Arieti and Gray[11] who reported a case in which an arteriovenous angioma of the brain was present together with aneurysms of the circle of Willis and abdominal aorta, and a condition described as "diffuse multiform angiosis" of the meningeal and cortical vessels.

One patient in the present series suffered from multiple hereditary haemorrhagic telangiectasia, and there can be little doubt that the acute episode of haemorrhage into the subarachnoid space which she experienced was the result of this syndrome.

Case 251.—A shop assistant aged 18 was admitted to the Royal Victoria Infirmary on March 31, 1944. She had been well until six weeks before when she had suffered a "fainting attack," and on recovering her senses had severe pain in the back of the neck; within 12 hours severe generalized headache developed and she went to bed. Her symptoms disappeared within a few days and after three weeks' rest she returned to work. Five days before admission she was again seized with a sharp pain in the back of the neck. Within a few moments she collapsed on the floor and had several generalized convulsions. Consciousness returned within an hour of onset, but occipital headache and pain in the back were severe and continued up to the time of admission.

Her previous health had been good and she had suffered no episodes of bleeding. Her mother had familial haemorrhagic telangiectasia and had bled from the mouth and nose and occasionally from the fingertips. Her maternal grandmother died from a stroke at the age of 32, her brother died of epilepsy at the age of 39, and a sister of 43 died of cerebral haemorrhage after suffering repeated nose-bleeds for several years.

On examination the patient was conscious and rational though drowsy; there was severe neck stiffness and Kernig's sign was strongly positive on both sides. The optic fundi showed occasional small haemorrhages, but there were no abnormal signs in the central nervous system. No telangiectases were noted in the skin, but a few small distended vessels could be seen in the tongue and buccal mucosa. The pulse was 68 per minute, blood pressure 100/65 mm. Hg and the temperature was 99.0° F., rising to 99.6° F. after four days. A lumbar puncture five days after the onset of the complaint revealed deeply bloodstained fluid; the pressure was not recorded; on centrifuging the supernatant fluid was yellow. Lumbar puncture produced slight improvement in her headache. She improved rapidly, being completely free from symptoms on April 17, and was discharged from the hospital four days later.

She remained in bed for between three and four weeks at home and then gradually resumed normal activity, being symptom free. When seen on June 13, 1944, she felt well and there were no haemorrhages in the optic fundi.

She remained well until July 10, 1944, when she awoke with pain in the back and found that her left leg was stiff and useless; later the same day the right leg became weak and she was unable to walk. On examination on July 17 she showed signs of a spastic paraplegia, the weakness being more severe on the left side; there was sensory loss to all modalities up to the area of the seventh thoracic segment. A myelogram showed a complete block at the ninth dorsal level; it was presumed that an intramedullary haemorrhage had occurred. A course of deep roentgen therapy was given to the ninth segment of the cord without obvious effect.

Slow clinical improvement occurred and the patient became able to walk; however, a further episode occurred in June 1947, producing signs of almost complete cord transection, and this time recovery was slight, the patient remaining bedridden. After a period of nursing at home in 1948 severe bedsores developed and readmission to hospital was required for blood transfusion and skin grafting. The patient's physical condition has slowly improved, and in July 1951 after prolonged physiotherapy she was able to walk a few steps despite a persisting severe paraplegia.

2. *Arterial rupture without aneurysmal formation.*

Many reported series of cases of subarachnoid haemorrhage refer to an occasional patient in whom subarachnoid bleeding was due to rupture of an

atherosclerotic artery at the base of the brain. Single cases of this nature have been described.[12,13,14] Rupture of so-called atherosclerotic aneurysms has been discussed elsewhere;[3] many authors have pointed out that these fusiform dilations of vessels are not aneurysms in the strictest sense of the term. In one patient in the Newcastle series a fatal attack of subarachnoid haemorrhage was shown to be due to rupture of an atherosclerotic vessel which showed no evidence of local dilatation.

Case 184.—A widow aged 73 collapsed suddenly on August 26, 1943, while having her eyes tested in the out-patient department of the Royal Victoria Infirmary. On admission to a medical ward half an hour later she was semicomatose, responding only to painful stimuli. Neck stiffness was marked and Kernig's sign was positive. There was a complete left third nerve palsy; both optic fundi showed advanced atherosclerosis and numerous flame-shaped haemorrhages, but there was no papilloedema and no subhyaloid haemorrhages were seen. All four limbs were rigid and the plantar responses were extensor. The blood pressure was 235/130 mm. Hg. Lumbar puncture three hours after the onset revealed a deeply bloodstained fluid under a pressure of 40 mm.; on centrifuging, the supernatant fluid was clear. The patient rapidly became comatose and died eight hours after admission.

At autopsy the following day there was a massive effusion of blood into the subarachnoid space at the base of the brain; the left third nerve was embedded in clot and the haemorrhage had penetrated the left side of the midbrain. There was a longitudinal tear in the trunk of the left internal carotid artery, which showed gross atheroma, as did the other vessels of the circle of Willis.

In the series of cases reported by Taylor and Whitfield,[13] one patient died from a subarachnoid haemorrhage which resulted from rupture of apparently healthy vessels at the bifurcation of an internal carotid artery. Such an event is extremely uncommon, although a similar case, that of a serving man who collapsed after following his master's chariot, was described by Morgagni[15] in his immortal "De sedibus et causis morborum per anatomen indagatis"; autopsy showed that bleeding had arisen from the lacerated trunk of the internal carotid artery. It is possible, indeed probable, that in these cases a small aneurysm was present whose sac was destroyed by the force of the haemorrhage. In an apparently similar case in the Newcastle series (case 93) where naked eye inspection suggested that a normal artery had ruptured, careful histologic examination of the artery at the site of rupture revealed a tag of fine fibrous tissue which was almost certainly a remnant of aneurysmal wall; the media of the artery stopped abruptly at this point.

3. *Intracranial neoplasms.*

The appearance of blood in the cerebrospinal fluid of patients with intracranial tumours has been commented upon by many authors.[16,17,18,19] In addition there has been an impression that sudden death or deterioration in cases of brain tumour may be brought about by rapid haemorrhage into the tumour substance; if blood were then to reach the subarachnoid space, the presenting clinical picture might be that of spontaneous subarachnoid haemorrhage. Clearly this chain of events is uncommon; of the 124 cases of subarachnoid

haemorrhage reviewed by Symonds[2] only two could be attributed to intracranial tumour or cyst, while Meadows[4] has said that bloody cerebrospinal fluid is rarely seen in patients with intracranial tumour, except if the neoplasm is a haemangioblastoma. Globus and Sapirstein[20] studied 94 cases of cerebral tumour and found that 15 died suddenly, but in none of these could death be attributed to haemorrhage. Bleeding into a tumour did occur in nine cases but did not produce specific symptoms and only once was the cerebrospinal fluid xanthochromic. There was, however, some evidence of subarachnoid bleeding in 21 patients; the tumours concerned included nine gliomas, two intraventricular tumours, one neurinoma, two pituitary adenomas, one meningioma and six metastatic carcinomas. In the majority of these cases the cerebrospinal fluid showed xanthochromia only or scanty red blood cells were seen on microscopy, but in a small number it was frankly bloody; this was noted particularly in the patients with metastatic carcinoma.

(a) *Glioma.* Profuse subarachnoid haemorrhage occurs rarely as the first manifestation of a cerebral glioma.[21,22] Single cases in which there were attacks of bleeding into the subarachnoid space have been reported.[23,24,25,26] In the case reported by Echols and Rehfeldt[26] the bleeding was particularly profuse and occurred repeatedly during two months of observation before operation; on exploration a glioblastoma of the frontal lobe was found. The rarity of episodes of this nature is stressed by the experience of Henderson and Gutierrez-Mahoney;[27] in reviewing the cerebrospinal fluid findings in 125 cases of cerebral glioma, they do not mention bloodstaining of the fluid. However, in seven of their cases there was xanthochromia and these patients were all shown to have glioblastomas, usually in close proximity to the ventricles.

One patient in the present series was shown to have a cerebral glioma.

Case 176.—A railwayman aged 63 was admitted to the Royal Victoria Infirmary on June 18, 1943. Until a year before admission he had been perfectly well, but since that time he had suffered several attacks of sudden loss of consciousness with convulsive movements of the limbs. For a few months there had also been very slight weakness and clumsiness of the left arm and leg, but he had been free from headache. On the day of admission he collapsed in the street and had a generalized epileptiform convulsion. On regaining consciousness an hour later, he complained of generalized headache.

On examination, two hours after the seizure, he was drowsy, confused and irritable. There was moderate neck stiffness and Kernig's sign was negative. The optic fundi were normal, as were the pupillary reactions. There was slight weakness of the left arm and leg and the reflexes on this side were increased, the plantar response being extensor. The pulse was 60 per minute; the blood pressure was not recorded; the temperature was 99.0° F. A lumbar puncture six or eight hours after the ictus revealed a deeply bloodstained fluid; the pressure was not recorded but on centrifuging the supernatant fluid was yellow. The patient remained confused, mentally unbalanced and difficult to control, and the left-sided weakness increased; he was transferred to the neurosurgical unit at the Newcastle General Hospital on June 29, 1943.

Ten days later the cranium was explored and a large inoperable glioma was found in the right frontal region. Histologic examination of a biopsy specimen suggests that it would

now be considered to be an astrocytoma, grade 3. The lesion was decompressed but the patient showed no improvement after the operation and was discharged from hospital on July 8, 1943. He died at home some five months later and no autopsy was performed.

(b) *Meningioma.* The author has been unable to discover any report of a clinically typical attack of subarachnoid haemorrhage arising from an intracranial meningioma, although Henderson and Gutierrez-Mahoney[27] remarked on the presence of faint xanthochromia in the cerebrospinal fluid of seven cases (in a series of 62), and Globus and Sapirstein[20] briefly mentioned one patient with a meningioma in whom the fluid was bloody. Vigneras[28] remarked on the presence of xanthochromic fluid in a patient with a spinal meningioma and assumed that bleeding had occurred previously, but this xanthochromia could equally have been due to a block in the spinal theca caused by the tumour.

One patient in the Newcastle series who suffered an attack of subarachnoid haemorrhage probably had a meningioma, but unfortunately the diagnosis was not proved.

Case 228.—A housewife aged 50 was admitted to the Royal Victoria Infirmary on March 19, 1941. She had been quite well until six years before admission when her left leg became numb and began to trail when she walked. These symptoms had gradually become worse and she also suffered from increasingly severe headaches in the right frontal and parietal regions. She had nevertheless been able to continue with her housework. One week before admission she was suddenly seized with violent frontal and occipital headache far more severe than any she had experienced previously. Her vision became "misted" and she began to vomit profusely. There was no loss of consciousness though she felt "hazy" and on looking to the right she saw double. On examination at admission, seven days after the onset, she was cooperative, though flushed, restless and dazed. There was severe neck stiffness and Kernig's sign was negative. The optic fundi showed severe bilateral papilledema, but the visual fields were normal, as were the pupillary reactions. Despite the diplopia there was no objective ocular paralysis. There were no abnormal signs in the upper limbs but a spastic monoparesis of the left leg was present and the left plantar response was extensor. The pulse was 80 per minute, blood pressure 155/85 mm. Hg, temperature 101.4° F. Lumbar puncture revealed a deeply bloodstained fluid under a pressure of 180 mm.; on centrifuging, the supernatant fluid was deeply yellow and contained 0.6 mg. per cent of bilirubin. An x-ray of the skull showed considerable thickening of the upper part of the right frontal bone with central erosion and increased vascular markings around this area; these findings were reported as being characteristic of meningioma. Lumbar puncture produced no improvement in the patient's condition; she became increasingly drowsy, neck stiffness increased and on March 31 she was comatose and showed signs of bilateral basal bronchopneumonia. Despite treatment she remained in coma and died on April 2, 1941. No autopsy was performed. In view of the history and the radiological changes it is probable that she had a meningioma in the upper part of the right frontal region.

(c) *Secondary carcinoma.* Madonick and Savitsky[29] have discussed the occurrence of subarachnoid bleeding in patients with metastatic tumours of the brain. In two of 56 verified cases seen at the Montefiore Hospital the cerebrospinal fluid was xanthochromic: in one the primary tumour was in the lung, in the other it was a hypernephroma. They also collected 56 cases of meta-

TABLE 2

CASES OF SPONTANEOUS SUBARACHNOID HAEMORRHAGE OF UNUSUAL AETIOLOGY OBSERVED IN THE NEWCASTLE SERIES

INTRACRANIAL ORIGIN					
*Case No.**	*Age*	*Sex*	*Aetiology*	*Method of confirmation*	*Comments*
251	18	F	Multiple hereditary haemorrhagic telangiectasia	Clinical	Subarachnoid haemorrhage apparently of intracranial origin. Subsequent paraplegia presumed to be due to rupture of similar lesion in cord
184	73	F	Ruptured atherosclerotic artery	Autopsy	Severe hypertension; longitudinal tear in grossly atheromatous internal carotid artery
176	63	M	Cerebral glioma	Exploration	In retrospect the previous history of fits and clumsiness of limbs should have suggested cerebral tumour. The correct diagnosis was not suspected before operation and neurological signs were felt to be due to intracerebral haemorrhage
228	50	F	Meningioma	Clinical	Death; no autopsy. Radiological changes in the skull were typical of meningioma. The history of headache and trailing of the leg pointed to the presence of a tumour before the haemorrhage occurred
192	43	M	Metastases of bronchogenic carcinoma	Clinical	Death; no autopsy. Few important symptoms before subarachnoid haemorrhage developed. Radiology revealed the presence of a bronchogenic carcinoma and of a deposit in the cervical spine. No evidence as to exact site of origin of bleeding
244	24	F	Metastases of malignant melanoma	Autopsy	The history and physical signs elsewhere than in the C.N.S. clearly indicated the aetiology of the bleeding
136	35	F	Aplastic anaemia	Autopsy	Aplastic anemia due to colchicine; attack developed 48 hours after blood transfusion. At autopsy there was massive haemorrhage in the right cerebellar hemisphere, rupturing into 4th ventricle. Aplastic bone marrow
312	43	M	Aplastic anaemia	Autopsy	Under treatment with blood transfusions for 2 years. Haemorrhage found in left parietal lobe rupturing through surface and into lateral ventricle. No bleeding point demonstrated. Aplastic bone marrow
50	38	F	Thrombocytopenic purpura	Clinical	Good recovery; the diagnosis of subarachnoid haemorrhage is irrefutable despite the absence of blood in the C.S.F. 3 days afterwards. Successful splenectomy later

TABLE 2—(Continued)

Case No.*	Age	Sex	Aetiology	Method of confirmation	Comments
133	5 months	F	Superior sagittal sinus thrombosis	Autopsy	The natural history of the illness and the overt otitis media in an infant suggested otitic hydrocephalus and this indicated venous thrombosis as the cause of the bleeding
39	58	M	Purulent meningo-encephalitis	Autopsy	Pyaemia, ulcerative endocarditis. Subarachnoid haemorrhage was the presenting feature of the illness; the coexistence of high fever and of cardiac murmurs indicated the inflammatory basis
131	20	M	Infective embolism in subacute bacterial endocarditis	Autopsy	Under treatment for bacterial endocarditis. Massive intracerebral and subarachnoid haemorrhage with no formation of mycotic aneurysms
220	24	F	Infective embolism in subacute bacterial endocarditis	Autopsy	The endocarditis had already been diagnosed and haemorrhage was not the presenting feature. Bleeding arose in a lateral lobe of the cerebellum; no mycotic aneurysms found
303	64	F	Scurvy	Clinical	Patient lived alone on a poor diet. On admission she was emaciated and showed purpura on the limbs and in the gums. Blood count normal. Death before the diagnosis of scurvy could be confirmed
			SPINAL ORIGIN		
158	49	F	Arteriovenous angioma of cord	Exploration	Symptoms were present before the haemorrhage but were misinterpreted. Subsequent paraplegia suggested intramedullary haemorrhage had occurred as well. Chronic urinary infection. Death
292	43	F	? Vascular anomaly of cord	Clinical	No prodromal symptoms. Temporary cauda equina syndrome after haemorrhage. Complete recovery; no residua 8 years later

*Case numbers are those allocated to the patients concerned in the series reported elsewhere;[8] cases are listed here in the order in which they are referred to in the text.

static brain tumour from the literature and of these six had bloody or xanthochromic fluid; in all six the primary tumour was bronchogenic. Merritt and Fremont-Smith[30] similarly remarked on the presence of bloody cerebrospinal

fluid in three of 27 patients with cerebral metastases and Henderson and Gutierrez-Mahoney[27] mentioned that of eight cases (seven bronchogenic, one hypernephroma) the fluid was xanthochromic in one.

Clearly bleeding into the subarachnoid space occurs appreciably often in patients with metastatic carcinoma of the brain, particularly when the primary neoplasm is in the lung; in view of the pleomorphic clinical picture produced by secondary deposits in the central nervous system such cases may well be confused with subarachnoid haemorrhage of other aetiology.

An attack of subarachnoid haemorrhage was probably caused by cerebral metastases of bronchogenic carcinoma in one patient in the Newcastle series.

Case 192.—A metal worker aged 43 was admitted to the Royal Victoria Infirmary on January 30, 1941. For some months he had had occasional vague generalized headaches but had been able to work until seven weeks before admission. He then developed a troublesome, irritating cough and pain in the left side of the chest. Five weeks previously his neck had become stiff and painful on movement and this stiffness had increased. On the day before admission, the pain in the neck became very severe and he developed an intense frontal and occipital headache.

On examination at admission he was drowsy and irritable and resented interference. He was pale and had clearly lost weight. There was definite neck rigidity and any movement of the head was painful; Kernig's sign was negative. The optic fundi were normal, and there were no abnormal signs in the central nervous system. The pulse was 110 per minute, blood pressure 120/60 mm. Hg, temperature 103° F. The chest showed diminished movement on the left side with poor air entry at the left base. Lumbar puncture performed two hours after admission revealed a deeply bloodstained fluid; the pressure was not recorded but on centrifuging the supernatant fluid was yellow. An x-ray of chest showed collapse of the left lower lobe with a dense root shadow; the appearances were typical of bronchogenic carcinoma. X-ray of cervical spine showed changes clearly due to an osteolytic metastasis in the body of the third cervical vertebra. The patient's condition deteriorated; he gradually lapsed into coma and died on February 6. No autopsy was performed, but it was considered that the subarachnoid hemorrhage had arisen from cerebral metastases of bronchogenic carcinoma and not from the deposit in the cervical spine.

(d) *Malignant melanoma.* Malignant intracranial melanomata, either primary or secondary, may give rise to subarachnoid bleeding so sudden as to cause confusion with aneurysmal rupture. Schnitker and Ayer[31] reviewed the literature on the primary melanomata of the meninges and added a case of their own; in 12 cases, the cerebrospinal fluid was grossly bloody in three and xanthochromic in two. Garin, Plauchu and Masson[32] reported four attacks of subarachnoid haemorrhage (hémorragie méningée à allure paroxystique) in a patient who had a melanocarcinoma of the jaw with multiple metastatic deposits in the meninges and brain, and Loewenberg,[33] in an extensive review, discussed 14 cases of metastatic melanoma of the brain (six observed personally); the fluid was bloody in several cases and xanthochromic in seven. Wortis and Wortis[34] have suggested that if bloody cerebrospinal fluid is found in a patient with melanomatous tumours of the skin, the fluid should be carefully examined for the presence of melanin pigment or mela-

noma cells. In the most recent review of this subject[29] five new cases of subarachnoid haemorrhage from metastatic melanoma are reported, of which one had melanin in the cerebrospinal fluid and also melanuria; these authors have reviewed the extensive literature and have shown that the cerebrospinal fluid was bloody or xanthochromic in 16 of the 35 proven cases of metastatic melanoma of the brain which have been reported. When the primary cases of Schnitker and Ayer[31] are added it will be seen that there was evidence of subarachnoid bleeding in 26 (46 per cent) of 56 cases of intracranial melanoma.

One patient in the present series developed subarachnoid haemorrhage as a result of metastatic deposits of malignant melanoma in the brain (case 244).

Case 244.—A nurse aged 24 was admitted to the Royal Victoria Infirmary on March 15, 1940. All her life she had had a small dark-coloured nodule in the small of her back, but two years before admission it began to bleed whenever it was touched. In June 1939 the nodule was clearly becoming larger and a surgeon was consulted; since the appearances were those of malignant melanoma the lesion was excised widely. The patient remained well until the beginning of February 1940 when she found that she was easily tired; soon afterwards small lumps began to appear beneath the skin all over her body. Two days prior to admission she experienced a brief attack in which she lost the power of speech; after ten minutes it returned and she felt quite normal again. Next day, however, aphasia returned suddenly when she was returning home from the cinema, and sudden severe occipital headache developed. Almost immediately she fell to the ground in a generalized epileptic convulsion, and from that time until her admission some 12 hours later she remained unconscious.

On examination at admission she responded only to painful stimuli; these produced withdrawal and she would roll over on to her left side as if resenting interference. There was marked neck stiffness and Kernig's sign was negative; the optic fundi were normal as were the pupil reactions and the other cranial nerves. The left leg showed less movement than did the other limbs and the tendon reflexes in this limb were absent. The left plantar response was extensor. She was incontinent of urine and faeces. The skin of the chest wall showed multiple small hard subcutaneous nodules; the liver was enlarged to three finger-breadths beneath the costal margin and was hard and nodular. The pulse was 72 per minute, blood pressure 120/80 mm. Hg, temperature 101° F. A lumbar puncture shortly after admission revealed a cloudy yellow fluid under a pressure of 250 mm.; on centrifuging there was a considerable deposit of red blood cells and the supernatant fluid was yellow. Coma gradually deepened until on March 18 she became completely unresponsive and her temperature rose to 103° F.; deterioration continued and she died on March 21, 1940.

At autopsy the next day the brain showed faint blood staining over the basal meninges but no site of bleeding was evident. Multiple small metastases of malignant melanoma, varying in size from a pinpoint to 1.1 cm. in diameter, were seen over the cortex and meninges. On dissection of the brain, many hundreds of deposits were noted and 55 were counted in one coronal section. The maximum number were seen at the junction of the grey and white matter, especially in the cerebellum, and there were also large numbers in the basal ganglia. Other multiple metastases were noted in the liver, ovaries, subcutaneous fat, vertebrae, myocardium, pleura and spleen; histologic examination showed the characteristic appearances of malignant melanoma.

(e) *Osteochondroma of base of skull.* Osteochondromas of the base of skull are very rare. King and Butcher[35] reviewed eight published cases and

reported another; they pointed out that these tumours usually encroach upon cranial nerves and the optic pathways and often give rise to hydrocephalus. However, in their case no signs of this nature were present; the first important clinical manifestation was a fatal attack of subarachnoid haemorrhage, although the tumour had been discovered previously on radiologic examination. Northfield and Russell[36] mentioned that death due to subarachnoid bleeding occurred in two cases of basal osteochondroma observed by them; one of the patients had Ollier's dyschondroplasia and chondromas of one upper extremity in addition to the intracranial growth. No case of subarachnoid haemorrhage arising in this way was observed in the Newcastle series.

(f) *Pituitary adenoma.* It is not generally recognized that a sharp attack of subarachnoid haemorrhage may be the first manifestation of a pituitary adenoma. These tumours are highly vascular, and it has been suggested (List, Williams and Balyeat[37]) that the growth rate of the neoplastic cells may outstrip their blood supply, thus producing infarction. When this occurs the tumour becomes a rapidly-swelling haemorrhagic mass which may produce profuse bleeding into the subarachnoid space and compression of neighbouring structures, particularly the optic pathways and oculomotor nerves. Dingley[38] reported the case of a man who dropped dead after running for a moving bus; the patient's previous health was excellent but autopsy revealed massive haemorrhage into a pituitary adenoma. Occasionally, as in the case described by Kirshbaum and Chapman[39] in which symptoms of acromegaly had been noted for 20 years, there may be clinical pointers to the nature of the aetiologic lesion. However, Brougham, Heusner and Adams,[40] who described five cases and entitled the syndrome "pituitary apoplexy," remark that this is uncommon. Three additional cases have been reported by List, Williams and Balyeat[37] and in two of these at least, the clinical picture, with sudden headache, neck stiffness, unilateral visual impairment and a third nerve palsy, was identical with that typically produced by rupture of a supraclinoid aneurysm of the internal carotid artery. The true nature of the underlying lesion was not appreciated until "ballooning" and erosion of the sella was noted radiologically.

No case of subarachnoid haemorrhage due to tumour of the pituitary was seen in the series under review, but a case showing some resemblance to the syndrome described has been observed since the study was completed.

A company director aged 51 was admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, on June 10, 1951. One week before admission he developed a severe frontal headache which improved after a day in bed; five days later headache returned, became increasingly severe and was accompanied by repeated vomiting. On the day before admission the right eyelid drooped, he became confused and had three generalized convulsions, beginning with jerking of the right limbs. On admission he was comatose; there was severe neck stiffness, right sided ptosis and the right pupil was widely dilated. All four limbs were flaccid and the right plantar response was extensor. He deteriorated rapidly and died before lumbar puncture could be performed; it was felt that he had had a subarachnoid haemorrhage from an aneurysm lying in relation to the right third nerve. At autopsy there

was no subarachnoid haemorrhage although meningeal veins at the base were grossly engorged. The sella turcica was expanded by a soft, haemorrhagic tumour 2.2 x 2.4 x 2 cm. in diameter, which was bulging upwards into the interpeduncular space and compressing the floor of the third ventricle; on histologic examination it was shown to be a chromophobe adenoma.

Comment: Despite the absence of subarachnoid haemorrhage the course of events and pathologic findings were typical of "pituitary apoplexy." The only feature lacking was rupture of the haemorrhagic tumour into the subarachnoid space. This case does, however, indicate that as in Dingley's[38] case, haemorrhage into the growth alone can have fatal results.

4. *Blood dyscrasias.*

The many blood diseases which have been complicated by subarachnoid haemorrhage include haemophilia,[41,42] pernicious anaemia,[43] "anémie splénomégalique",[44] aplastic anaemia, leukaemia and agranulocytosis,[17] thrombocytopenic purpura,[13,17,45] polycythaemia vera,[16] and sickle cell anaemia.[46,47]. In a case of purpura haemorrhagica described by Gitt and Weiss[48] subarachnoid haemorrhage was the primary manifestation of the underlying disease. Probably subarachnoid bleeding occurring during anticoagulant therapy[49] should also be mentioned here. In blood diseases as a whole the prognosis of subarachnoid haemorrhage tends to be poor; of ten reported cases occurring in sickle cell anaemia, for instance, four have survived, one is mentally defective and two were left with a residual hemiplegia. It appears that in such cases subarachnoid haemorrhage may occasionally herald or provoke the onset of meningitis; in the 11 year old boy with sickle cell anaemia reported by Almklov and Hansen[46] the haemorrhagic episode was followed by staphylococcal meningitis. A somewhat similar occurrence has been described by Nelson-Jones;[50] a patient developed brucellar meningitis directly after a subarachnoid haemorrhage, presumed to have arisen from rupture of an aneurysm.

Three patients with subarachnoid haemorrhage as a result of blood disease are included in the present series, namely two cases of aplastic anaemia (cases 136 and 312), previously reported by Boon and Walton[51] and one case of thrombocytopenic purpura (case 50).

Case 50.—A domestic servant aged 38 was admitted to the Royal Victoria Infirmary on April 22, 1948. For some time she had bruised severely on slight trauma and had had irregular and profuse vaginal bleeding. Investigation revealed typical blood and bone marrow findings of purpura haemorrhagica, in that the platelet count in the peripheral blood was less than 30,000 per cu. mm. and profuse megakaryocytes, none of which was producing platelets, were seen in a specimen of sternal marrow. Further, there was definite clinical splenomegaly. She was admitted, given two pints of compatible packed cells over an eight hour period, and discharged two hours later. Next morning on waking she noticed a slight generalized headache which increased as the day wore on and eventually became severe, particularly in the occipital region and in the back of the neck. This headache continued and on April 26, 1948 she was re-admitted to the hospital.

On examination she was conscious and rational though apprehensive. There was severe neck stiffness and Kernig's sign was positive. The pulse was 68 per minute, blood pressure 135/80 mm. Hg, temperature 99.2° F. There were no abnormal signs in the central nervous system but the limbs showed numerous ecchymoses. A lumbar puncture

carried out three days after the onset of the headache revealed a clear, brightly yellow fluid under a pressure of 120 mm. Haemoglobin was 79 per cent, (11.45 g. per 100 ml.), platelets 30,000 per cu. mm.

She improved rapidly and on May 18 splenectomy was carried out; postoperative progress was uneventful. She remained free from symptoms and three months after the operation went back to work. Since then she has had occasional headaches; she has continued to bruise easily but has had no profuse bleeding. In addition to doing all her own housework, she works as a charwoman.

5. *Intracranial venous thrombosis.*

Gintrac[42] drew attention to the occurrence of meningeal haemorrhage in patients with thrombosis of the superior sagittal sinus, and subsequently Hayem,[52] Froin[53] and Ingvar[54] referred to this association. Additional cases have been reported;[17,55] Klein and Lederer[56] described a similar case in which profuse subarachnoid haemorrhage occurred and at autopsy there was thrombosis of the right lateral sinus and internal jugular vein resulting from acute mastoiditis. Probably in these patients the subarachnoid haemorrhage arises as a result of cortical infarction, and it is perhaps surprising that the association is not more common. For instance, Kendall[57] described 11 cases of intracranial venous thrombosis of which five occurred during pregnancy and six were of infective origin; in only one case was there blood in the cerebrospinal fluid.

A case of subarachnoid haemorrhage in the present series, arising in an infant of five months, was shown at autopsy to be due to thrombosis of the sagittal sinus resulting from acute otitis media.

Case 133.—A female infant aged five months was admitted to the Royal Victoria Infirmary on December 8, 1947. Seven days before admission the mother had noticed some purulent discharge from the right ear. From that time, the child had gradually become listless and drowsy, was eating poorly and cried if handled. The child began to vomit and as the days progressed she became apathetic and more deeply drowsy. There were no convulsions but the mother "thought that she was going to have one."

On examination she was a drowsy, apathetic but irritable baby who screamed if disturbed. There was definite neck stiffness and the right ear was clearly the seat of acute otitis media. The pulse rate was over 200 per minute and the temperature 103° F., later rising to 105° F. The optic fundi showed severe bilateral papilloedema, but no other abnormal signs were recognized in the central nervous system. A lumbar puncture revealed deeply bloodstained fluid under increased pressure; on centrifuging the supernatant fluid was yellow and its protein content was 150 mg. per cent.

The child was treated with systemic penicillin, but on the day of admission she began to have repeated convulsions in which all four limbs went stiff and the head and eyes turned to the right. These attacks recurred persistently for three days despite intramuscular paraldehyde and she died on December 12.

At autopsy the presence of otitis media in the left ear was confirmed. Extensive subarachnoid haemorrhage was seen over the convexities of the brain. There was widespread thrombosis of cortical veins bilaterally with haemorrhagic infarction of the superior surfaces of both hemispheres, particularly the frontal lobes. The superior sagittal sinus was filled with antemortem clot and numerous swabs from this blood clot failed to grow organisms although the Friedlander bacillus was grown from a swab taken from the pus in the left middle ear.

6. *Inflammatory conditions of brain and meninges.*

The early French authors[42,52,53,54] described the association of subarachnoid haemorrhage with acute bacterial infections, infective fevers, anthrax, meningitis and meningoencephalitis. Schonfeld[58] reported the case of a child of 14 months with multiple renal calculi and a perinephric abscess; a fatal attack of subarachnoid bleeding occurred and purulent meningoencephalitis was discovered at autopsy, but since there was also thrombosis of both lateral sinuses and of some cortical veins, the bleeding may have arisen from cortical infarction. Sands[17] referred to cases in which tonsillitis, meningococcal septicaemia and a brain abscess, respectively, were complicated by the occurrence of subarachnoid haemorrhage which was so severe as to obscure the underlying disorder. An example of subarachnoid bleeding in a patient with the Friderichsen-Waterhouse syndrome due to meningococcal septicaemia has been reported recently by Breen, Emond and Walley.[59] It is probable that in cases of this nature a large vessel or numerous small vessels are eroded by the fulminating inflammatory process. The tuberculous arteritis which occurs in tuberculous meningitis has resulted in subarachnoid haemorrhage[60] and localized dilatations in meningeal vessels under such circumstances have been observed.[61] However, scrutiny of recent reports of large series of cases of tuberculous meningitis has failed to reveal instances of this complication and Doniachi[62] and others have shown that the arteritis usually results in thrombosis and vascular occlusion, so that infarction and not haemorrhage is the rule. On the other hand Somner[63] has reported severe bouts of haemorrhage occurring as a response to cisternal injections of streptomycin in a case of tuberculous meningtis. Vascular erosion may also occur in luetic meningoencephalitis,[64,65] but syphilis is rarely an aetiologic agent in subarachnoid haemorrhage, despite assertions to the contrary by Ungerman and Lowbeer[66] and others. It is of interest that the arteritis produced by aspergillosis of the brain has been known to produce a typical sharp attack of subarachnoid haemorrhage.[67] Similar attacks have been described in relapsing fever,[68,69] but the case figuring in the latter report was also suffering from haemorrhagic nephritis; this raises the possibility that the bleeding was not due to the primary infection but rather to generalized vascular changes.

No case of subarachnoid bleeding due to infective fevers, brain abscess, syphilis, or tuberculous meningitis was seen in the Newcastle series, but one patient admitted with an attack of subarachnoid haemorrhage was found to be suffering from purulent meningitis, pyaemia and acute ulcerative endocarditis.

Case 39.—A cabinetmaker aged 58 was admitted to the Royal Victoria Infirmary on March 4, 1948. Two months earlier he had developed bilateral ear discharge which cleared up in two weeks under treatment from his general practitioner. One week before admission, however, both ears began to discharge thick yellow pus. Two days later he came home from work feeling dizzy and complaining of severe headache which had come on gradually, beginning in both temples and passing down the back of the neck.

On examination he was drowsy and clearly ill and both cheeks showed a hectic flush; there was severe neck stiffness and Kernig's sign was positive bilaterally. The pulse was 112 per minute and collapsing in type, the blood pressure 150/70 mm. Hg and the temperature on admission 104° F. The ocular fundi were normal; the right pupil was larger than the left, although both reacted to light and accommodation. There were no other abnormal signs in the cranial nerves or extremities. Examination of the cardiovascular system showed the heart to be enlarged, the apex beat being in the sixth interspace, four inches from the midline. No thrills were noted but systolic murmurs were heard at the apex and at the base and there was a diastolic murmur in the aortic region which was conducted down the left border of the sternum. Lumbar puncture was performed six days after the onset of the illness and showed deeply bloodstained fluid under a pressure of 250 mm.; on centrifuging, the supernatant fluid was yellow. A smear of the fluid suggested that an excessive number of polymorphonuclear leucocytes was present. The Wassermann reaction in the cerebrospinal fluid was positive. The urine contained a small quantity of albumin and occasional red and white cells.

A clinical diagnosis was made of acute bacterial endocarditis with subarachnoid haemorrhage; it was felt that there was a possibility of early suppurative meningitis. Accordingly treatment was begun with systemic and intrathecal penicillin. Intravenous glucose saline therapy was also given and paraldehyde was administered intramuscularly for sedation; 12 hours later auricular fibrillation supervened and was treated by means of 1 mg. of Digoxin intravenously. Despite treatment the patient deteriorated steadily; after 24 hours he became wildly delirious and died 48 hours after admission.

At autopsy, the heart showed the appearances of syphilitic aortitis with acute ulcerative endocarditis on the aortic valve. Small pyaemic abscesses were found in the lungs, liver and spleen and in the kidneys in particular. The brain showed profuse blood clot around the base and in the ventricles and there was a fine purulent exudate over the vertex. There were numerous cortical infarcts in the cerebrum and cerebellum and multiple tiny pyaemic abscesses were noted in the cerebral substance; one of these appeared to have eroded a blood vessel in the posterior horn of the left lateral ventricle. A culture of the pus from an abscess gave a growth of staphylococcus aureus. There was no histologic evidence of syphilis of the central nervous system.

It is well known that subarachnoid haemorrhage may occur during the course of subacute bacterial endocarditis; usually the syndrome results from rupture of a mycotic aneurysm on one of the cerebral arteries and frequently such an event ends fatally. Rarely an attack of subarachnoid bleeding may develop as the presenting symptom before other evidence of the disease has been recognized. This was the course of events in the cases described by Stein[70] and Starrs;[71] the former, a girl of nine years, died while the latter, a woman aged 22, recovered. Recovery has occurred in one other case only, that reported by Graves and Russell;[72] it should, however, be mentioned that the diagnosis of subacute bacterial endocarditis in this patient, though likely, was not irrefutable. Additional fatal cases, usually occurring late in the course of the endocarditis, have been described.[73,74] Rupture of mycotic aneurysms has been discussed elsewhere by the author[3] and so will not be considered here; however, in certain patients with bacterial endocarditis who die of cerebral vascular accidents, no arterial dilatation can be demonstrated. Frequently the haemorrhage is primarily intracerebral with spread to the subarachnoid space, and Martland[15] has suggested that often it is produced through the general toxic effect of the disease upon the vessel wall. It is

equally possible that an infected embolus might cause a sudden breach in an artery, instead of giving rise to the slower process of aneurysmal formation. Whatever the exact pathogenesis, there is little doubt that occasionally subarachnoid haemorrhage complicating subacute bacterial endocarditis does not depend upon aneurysmal formation.

In the Newcastle series, four patients with subacute bacterial endocarditis died of subarachnoid haemorrhage; in two, ruptured mycotic aneurysms were found, but in the other two cases, reported below, the haemorrhage appeared to begin in the cerebral or cerebellar parenchyma, with extension to the subarachnoid space, and no bleeding point could be demonstrated. Despite the site of origin of the haemorrhage in these two cases, the clinical picture in each was considered to be that of spontaneous subarachnoid haemorrhage.

Case 131.—A male clerk aged 20 was admitted to the Royal Victoria Infirmary on August 12, 1945, and was found to be suffering from subacute bacterial endocarditis. Treatment with systemic penicillin had been in progress for over a week, when suddenly, on September 1, 1945, the patient cried out, began to retch violently and perspired profusely. Within half an hour he was comatose. Neck stiffness was noted almost immediately, and there was a complete right-sided third nerve palsy. The limbs were flaccid, although the tendon reflexes appeared to be exaggerated in the left arm; both plantar responses were extensor; the patient's condition deteriorated rapidly and he died four hours later. Lumbar puncture was not performed but it was felt that a catastrophic subarachnoid haemorrhage had occurred.

At autopsy the next day, the left cerebral hemisphere was found to be extremely soft; it was almost entirely occupied by an enormous blood clot which reached the surface of the brain by rupturing through the island of Reil; it was also continuous with clot in the left lateral ventricle which passed out into the subarachnoid space via the basal foramina. The haemorrhage in the brain substance reached to within 3.0 cm. of the frontal pole and 8.0 cm. of the occipital pole; it was 6.5 cm. in its maximum diameter. No bleeding point was discovered, and there were no mycotic aneurysms on the circle of Willis. Large infective vegetations were seen on the mitral and aortic valves, which were the seat of old rheumatic heart disease.

Case 220.—An unemployed girl aged 24 was admitted to the Royal Victoria Infirmary on January 12, 1945. She had been known since childhood to have a congenital heart lesion, but in the few weeks prior to admission she had become listless, increasingly breathless and had lost weight and appetite. Soon after admission a streptococcus viridans was grown on blood culture, and she was about to begin penicillin treatment when she suddenly collapsed and within a matter of seconds became comatose with stertorous respiration. There was marked neck stiffness, all four limbs were flaccid and the plantar responses were extensor. Lumbar puncture was not performed, but a clinical diagnosis of subarachnoid haemorrhage was made. The patient's condition deteriorated rapidly and she died 12 hours after onset of the attack.

At autopsy the next day, there was a well-marked cerebellar pressure cone; there was a large amount of clot in the basal cisterns, the largest amount being in the region of the posterior perforated substance. In the right lateral lobe of the cerebellum was a haemorrhage 4.0 x 4.0 x 1.0 cm. in diameter which had ruptured through the cortex just below the tentorium. No bleeding point was demonstrated, and the vessels of the circle of Willis and their branches were macroscopically normal. The heart showed a patent interventricular septum; typical vegetations of subacute bacterial endocarditis were present on the aortic and mitral cusps and on the infundibulum.

7. *Focal vascular necrosis.*

Kernohan and Woltman[75] reported four cases in which acute subarachnoid haemorrhage occurred in elderly hypertensive patients within a few days of uncomplicated abdominal operations. All were fatal and at autopsy the bleeding was found to have arisen from rupture of a vertebral artery in two cases and of a posterior inferior cerebellar artery in two. Histologic investigation revealed that rupture was the result of focal aseptic necrosis of the vessel wall; the authors suggested that it had occurred as a result of thrombosis of the vasa vasorum. No further cases of similar aetiology appear to have been reported and none was seen in the present series, although one severely hypertensive woman of 66 years (case 87) died of subarachnoid haemorrhage 14 days after an operation for strangulated femoral hernia. Unfortunately, no autopsy was performed. Case 35, a woman of 47, whose blood pressure was normal, developed a subarachnoid haemorrhage 13 days after a total hysterectomy but she made a good recovery; it is unlikely that pathologic changes of the type under discussion were the basis of her illenss.

8. *Polyarteritis nodosa and other vascular allergy.*

It is well recognized that the lesions of polyarteritis nodosa occasionally involve the cerebral vasculature[77,78,79] and subarachnoid haemorrhage occurring during the course of this disease has been described.[80,81,82,83] In addition, Miller[84] has described bleeding into the subarachnoid space in a case of anaphylactoid purpura (the Henoch-Schonlein syndrome). It is probable that a general allergic vascular response was responsible for the subarachnoid haemorrhage which occurred in the patients with haemorrhagic nephritis described by Sands,[17] Dewar and Walmsley[69] and Pedigo and Nolan;[85] in the two cases which came to autopsy the brain showed congestion and oedema but no focal bleeding point could be demonstrated. Similar vascular changes may have been present in the reported cases with subarachnoid bleeding developing during the course of acute rheumatism.[81,86,88]

None of the 312 cases of the present series was suffering from polyarteritis nodosa or other vascular allergy and in no case were such pathologic lesions found at autopsy. One patient (case 73, a man aged 29) was recovering from an attack of acute rheumatism when his subarachnoid haemorrhage occurred; he made a good recovery only to die of a recurrence of bleeding two months later. The rheumatism probably bore no relationship to his illness and it is more than likely that bleeding arose from rupture of an aneurysm or angioma. During the same period as that covered by this investigation, autopsies were performed on 15 cases of polyarteritis nodosa in the Royal Victoria Infirmary, and in 13 of these the brain was examined. In ten of the 13 cases the brain appeared normal macroscopically and histologically. Of the remaining cases, one showed a small area of subependymal haemorrhage in the occipital region, and another typical polyarteritic lesions in the vessels of the pons and midbrain. The only abnormality noted in the third case was an unruptured

"berry" aneurysm, 0.3 cm. in diameter, on the right middle cerebral artery; the artery showed no histologic evidence of polyarteritis. These findings suggest that cerebral vascular accidents must be relatively uncommon in polyarteritis nodosa and the third case shows that even in the presence of a disease known to cause subarachnoid bleeding, the occurrence of the latter could yet be due to rupture of an intracranial aneurysm of congenital origin.

9. *Miscellaneous disorders.*

Other agents apparently concerned in the aetiology of individual cases of subarachnoid haemorrhage include sunstroke,[89] scurvy and alcoholism,[16] insulin therapy and electroplexy,[90,91,92] pneumoencephalography,[17] Metrazol administration[93] and the injection of adrenaline.[94] Strauss and Tarachow[16] noted the presence of tuberculosis, diabetes and Hodgkin's disease respectively in certain of their cases of subarachnoid haemorrhage, and suggested an aetiologic relationship; it is possible, indeed probable, that the association was fortuitous. It is also doubtful whether sunstroke can now be considered of real importance. Damage of the cerebral vasculature by the other agents which have been quoted can be understood and occasional cases of such diverse aetiology will probably continue to arise.

In the present series an elderly female patient (case 303) who lived alone, probably had scurvy, but died before the diagnosis could be established; unfortunately no autopsy was performed. Several other patients had associated diseases such as tuberculosis, diabetes, syphilis and chronic alcoholism, but the available evidence suggests that these conditions bore no aetiologic relationship to the attack of subarachnoid haemorrhage.

SPINAL SUBARACHNOID HAEMORRHAGE

One of the first observations of subarachnoid haemorrhage confined to the spinal theca was that of Duverney[95] who, in 1688, described the case of an illustrious magistrate "mort presque subitement d'une éspèce particulière d'apoplexe qui ne lui avait pas ôté la connaissance." At autopsy the brain and its membranes were normal, but a large amount of blood clot filled the theca. A similar case was described by Duhamel,[96] and the subject was discussed extensively by Morgagni,[15] Boscredon[97] and Vigneras.[28] The latter author remarked that when such haemorrhages occurred spontaneously, they could often be attributed to syphilis, alcoholism or haemophilia, but in many cases it was impossible to ascertain the cause; other cases resulted from trauma, or were secondary to neoplasms of the cord or meninges. He reported one "spontaneous" case and discussed three others in which a vascular tumour, a meningioma and tuberculous disease of the spine were present respectively; it must be mentioned, however, that in these three cases there was no clear evidence of bleeding into the theca, since the fluid showed xanthochromia only, a finding which could equally have been due to spinal block produced by the space-occupying lesion.

Other cases of this syndrome have been described,[14,98,104] while other cases

have been reported[66,105,106] in which the origin of the haemorrhage may have been intracranial although the symptomatology of the illness suggested a considerable accumulation of the blood within the theca.

From the published reports it is clear that the illness usually begins with severe pain in the back, frequently spreading to the abdomen or down the legs, depending upon which nerve roots are most affected by the haemorrhage. There is often rigidity of the spine and even opisthotonus,[99] with marked hyperaesthesia in the distribution of the affected roots. Kernig's sign is always strongly positive. Characteristically there is no disturbance of the sensorium and no cerebral symptoms occur, but if the patient is recumbent, blood may flow into the basal cisterns giving rise to headache and neck stiffness. Urinary retention is usual, and occasionally the situation of the pain, which may be excruciating, gives rise to severe difficulty in diagnosis; Thurston's[106] case was at first thought to be suffering from an intra-abdominal catastrophe and in two of the cases described by Ungerman and Lowbeer[66] the symptoms resembled those of Deitl's crisis. Various paralytic signs may develop in the lower limbs; they may be lower motor neurone in type as in the case reported by Swoboda[103] or there may be signs of cord damage. Probably the presence or absence of cord involvement depends upon the nature and situation of the aetiologic lesion; for instance, the rupture of a vascular anomaly of the cord may produce intramedullary as well as subarachnoid haemorrhage. Severe contractures of the hamstrings occasionally develop,[28,105] presumably as a result of plastic meningitis around the cauda equina.

It is now clear that syphilis, alcoholism and the other varied aetiologic agents mentioned by Vigneras[28] are of little importance in the aetiology of this syndrome, although as recently as 1950 Swoboda[103] postulated diapedetic haemorrhages due to general fragility of vessels as a cause. However, evidence has accumulated that vascular tumours or malformations of the spinal cord or meninges such as anteriovenous angiomas, racemose venous malformations[107] or telangiectases[108] commonly underly the clinical syndrome under discussion. Rarely it may arise through rupture of a spinal artery.[14] Occasionally neoplasms other than angiomas may give rise to profuse subarachnoid bleeding; this occurred in two cases of intradural neurinoma reported by Krayenbuhl[102] and in cases of tumour of the cauda equina described by Thomas, Ferrand, Schaeffer and de Martel,[98] Abbott[101] and Fincher.[104] Fincher[104] remarked that in none of his five cases was there any intimation of motor, sensory or sphincteric disturbance before the haemorrhage occurred. Each patient had several attacks of bleeding with characteristic intractable lower extremity pain; three of the patients were shown to have ependymomas of the filum terminale as in Abbott's[101] case, while in the other two a neurofibroma and a neuroglioma (sic) were demonstrated respectively.

In two patients (0.6 per cent) of the Newcastle series, bleeding appeared to be confined to the spinal subarachnoid space; in one, an arteriovenous

angioma was seen in the spinal cord at operation; in the other the aetiology of the bleeding was unconfirmed, although the presence of a vascular anomaly seemed probable on clinical grounds.

Case 158.—A labourer aged 49 was admitted to the Royal Victoria Infirmary on November 13, 1945. He had been perfectly well until August of the same year when he had experienced gradually increasing difficulty in passing urine. He was seen by a surgeon and prostatectomy was performed at the end of August. This seemed to make little difference to his urinary symptoms, and soon afterwards he began to feel weak in the legs and developed pain of a girdle nature round the upper part of his back and chest. On the day of admission to this hospital, sudden severe pain appeared in the lower back and shot down the back of both legs. Soon afterwards flexor spasms of the legs developed. He was admitted to a surgical ward; his bladder was found to be grossly distended and an indwelling catheter was inserted. In view of the abnormal neurologic signs which were found in the lower extremities he was transferred to a medical ward.

On examination he was mentally clear and cooperative but complained of severe pain in the legs. There was no neck stiffness but Kernig's sign was strongly positive bilaterally.

There were no abnormal signs in the cranial nerves or upper limbs but there was a total flaccid paralysis of both lower limbs with loss of sensation of all modalities below the groins. The reflexes in the lower limbs were absent and both plantar responses were extensor. The pulse was 80 per minute, blood pressure 130/80 mm. Hg, temperature 103° F. A lumbar puncture performed six days after the onset of the illness revealed a bloodstained fluid under normal pressure and Queckenstedt's test gave a normal response. On centrifuging, the supernatant cerebrospinal fluid was deeply yellow, its protein content was 300 mg. per cent and it contained 16 lymphocytes per cu. mm. The urine contained pus cells but no other abnormal constituents. The indwelling catheter was retained in situ and sulphonamides and other urinary antiseptics were given. The pain and flexor spasms gradually subsided and he was transferred on November 22 to the Newcastle General Hospital.

X-rays of dorsal spine revealed no abnormality, there being no expansion of the interpedicular spaces. A myelogram revealed an apparently complete block to the passage of contrast medium at the fourth dorsal level. Laminectomy was performed on November 29, 1945 and a large angioma was discovered on the posterior surface of the cord extending between the fourth and eighth dorsal segments. This was clearly inoperable but the spinal canal was decompressed. A course of deep x-ray therapy was given with little improvement and the patient was transferred to a nursing home on December 28, 1945. He remained paraplegic and bedridden until his death in that institution one year later from a severe ascending urinary infection. Autopsy was not performed.

Case 292.—A married woman aged 43 was admitted to the Royal Victoria Infirmary on February 22, 1943. Two days before admission, while bathing her baby, she suddenly developed a severe pain in the lower part of her back which shot down the left leg. A few moments later the pain travelled down the back of the right leg. Within an hour the left leg became numb and useless and she was unable to stand; the right leg also became numb but there was no loss of power on this side. Pain in the back was continuous with occasional severe exacerbations passing down the legs, particularly the left, but the numbness improved and became confined to the left leg below the knee. There was also considerable difficulty in starting micturition.

On examination the patient was an excellent witness and there was no clouding of consciousness. There was no neck stiffness but Kernig's sign was positive bilaterally. There was a complete left foot drop, with impairment of sensation of all modalities below the knee, and the plantar response on the left side was absent. There were no other abnormal signs in the central nervous system. The pulse was 80 per minute, blood pressure 195/115

mm. Hg, temperature 99° F. The urine contained no abnormal constituents. A lumbar puncture performed two days after the onset of the illness revealed a deeply bloodstained fluid under a pressure of 60 mm.; on centrifuging, the supernatant fluid was yellow.

The patient's condition gradually improved spontaneously and by March 29 the sensory loss had receded to the ankle and the power was greatly improved, although there was still some weakness of dorsiflexion of the left foot. No myelogram was performed, but in view of the clinical impression that bleeding was probably due to an angioma, a course of deep x-ray therapy was given to the lower segment of the spinal cord. The patient was discharged from hospital on April 27, 1943, and could then walk the length of the ward.

For a few weeks she had a good deal of pain in both legs, with tightness of the hamstrings; some weakness of the left leg remained but she improved steadily.

After a year the power in the left leg and foot was normal although some numbness remained for about three years. She has since lived a normal life and when last seen on August 29, 1951 she had no complaints, and there were no abnormal signs on neurologic examination.

DISCUSSION

Although it is agreed that spontaneous subarachnoid haemorrhage usually results from rupture of an aneurysm or angioma it should not be assumed that this is invariable. Sixteen cases are reported, forming 5 per cent of a large series of patients with attacks of spontaneous subarachnoid bleeding, in which many diverse pathologic states were responsible for the haemorrhage. Clearly the lesions found in some cases, such as rupture of atherosclerotic arteries and focal vascular necrosis, are of pathologic interest only; however, when subarachnoid bleeding arises during the course of other important diseases, diagnosis of the nature of the underlying pathologic process is essential in order to formulate a rational plan of therapy. In most cases of the latter type in this series, symptoms or signs had been present before the acute attack, giving some indication of the nature of the aetiologic lesion; quite often these pointers were ignored owing to the dramatic manifestations of the subarachnoid haemorrhage. In only three of our cases was the haemorrhage the first important sign of another disease; this was so in the girl with familial telangiectasia, although the family history held the solution to the problem of aetiology. It was also the presenting feature in the patients with metastasing bronchogenic carcinoma and suppurative meningoencephalitis, although a few vague symptoms had been noted beforehand. In previous reports, subarachnoid haemorrhage has been the initial manifestation of the primary disease in cases of intracranial glioma,[21,22] melanoma of the meninges,[31] osteochondroma of base of skull,[35] pituitary adenoma[37,40] purpura haemorrhagica,[48] subacute bacterial endocarditis[70,71] and cauda equina tumour.[104]

It may be concluded that in any case of subarachnoid haemorrhage, symptoms and physical signs should be interpreted in the light of all the possible causes of the syndrome. To take a single example, sustained fever and malaise in a patient with cardiac murmurs might raise the possibility of the coexistence of subacute bacterial endocarditis. Other implications arising out of recent advances in therapy are too obvious to require discussion in detail. It would, for instance, be disastrous to embark on surgical treatment[109,110] in a patient

with, say, occult thrombocytopenic purpura. On the other hand, it would be equally unfortunate if a patient with a previously asymptomatic, surgically remediable, intracranial or intraspinal tumour were treated conservatively. If these points are borne in mind, it will sometimes be possible to reach the conclusion, after careful clinical examination, that a blood dyscrasia, vascular allergy, or infective embolism is the cause of bleeding. In other cases, however, accurate diagnosis will be impossible without recourse to ancillary investigations. Examination of the cerebrospinal fluid will have revealed the presence of blood; an excessive proportion of polymorphonuclear leucocytes may suggest the possibility of meningitis, or melanin in the fluid may indicate the presence of intracranial melanomata. Otherwise cerebrospinal examination is of little value for determining the cause of bleeding, except in cases of intrathecal haemorrhage, where signs of a block and a high protein may suggest an intrathecal neoplasm. Apart from examination of the blood, which will be indicated whenever the possibility of a blood dyscrasia arises, and blood culture, which will be required in cases of suspected infected endocarditis, the other investigations most likely to be of value are radiologic. Thus radiography of the skull may reveal a tumour of the base or expansion of the sella turcica due to a pituitary adenoma; or perhaps there may be changes in the vault indicating the presence of a meningioma or even metastases. It is also wise in such cases to take a radiograph of the chest to exclude the possibility of bronchial neoplasia with metastasis. Most important of all, however, is cerebral angiography; although contraindicated in cases with evidence of blood disease or generalized vascular pathology, this technique is fast becoming a routine investigation in cases of subarachnoid haemorrhage. Whereas it commonly reveals aneurysms or angiomas in such patients it is also likely to reveal gliomas or cerebral metastases in the rare cases in which bleeding is so produced. In those patients in whom the clinical picture suggests bleeding arising within the theca, myelography will invariably be indicated once the acute episode is over, since by this means remediable extramedullary neoplasms may sometimes be demonstrated.

Despite the undoubted value of the investigations mentioned they are sometimes negative and if this is so careful clinical appraisal of each case is of paramount importance in order to decide the nature of the causal pathology. This study has been reported as an appeal against the common assumption that all cases of subarachnoid bleeding arise from ruptured aneurysms or angiomas. The occasional presence in such patients of widely varying pathologic conditions, many of which require specific treatment, demands studious clinical observation of each individual case and the employment of appropriate investigations.

SUMMARY

The syndrome of spontaneous subarachnoid haemorrhage usually results from rupture of an intracranial aneurysm, or less commonly, a cerebral

angioma, but occasionally it may be produced by a variety of pathologic lesions of the central nervous system.

When the haemorrhage arises intracranially, aetiologic agents which may be implicated in occasional cases include telangiectases, intracranial neoplasms of many types, blood dyscrasias, venous sinus thrombosis, inflammatory conditions such as meningitis, abscess and infective emboli, focal vascular necrosis, vascular allergy, and miscellaneous factors including pneumoencephalography and insulin or Metrazol administration. Spinal subarachnoid haemorrhage is usually the result of vascular malformations of the spinal cord or meninges but can occasionally be produced by intrathecal neoplasms other than angiomas. Sometimes signs of the primary disease are evident when bleeding occurs but often haemorrhage may be the first manifestation.

Illustrative cases of unusual aetiology, comprising 5 per cent of a recently studied series of 312 consecutive cases of spontaneous subarachnoid haemorrhage, are reported and the relevant literature is reviewed.

The recognition of such cases is of importance since many of the conditions mentioned require specific treatment. Hence all possible causes should be considered in the observation of patients with subarachnoid haemorrhage; careful clinical appraisal of each case is of the greatest importance and any unusual features in the clinical picture may indicate the need for investigations other than those commonly employed.

I wish to thank the physicians of the Royal Victoria Infirmary, Newcastle upon Tyne, for permission to consult their records and to examine their cases. In particular I am grateful to Professor F. J. Nattrass for his encouragement and advice. I am also indebted to Mr. G. F. Rowbotham of the neurosurgical unit, Newcastle General Hospital, for permission to record details of surgical treatment. Finally I wish to acknowledge the help given by Miss Audrey Cairns and Mrs. J. Molyneux in preparation of the manuscript.

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The aura of an attack, *i. e.*, the sensation, usually in some part of the periphery, with which attacks commence, was formerly regarded as an actual process taking place in the part to which the sensation was referred, and commencing there. The word "aura" was first used by Pelops, the master of Galen, who was struck by the phenomena with which many attacks begin – a sensation, commencing in the hand or the foot, apparently ascending to the head. The sensation having been described to him by patients as a "cold vapor," he suggested that it might really be such, passing up the vessels, then believed to convey air. Hence he termed it "spirituous vapor." This notion of the peripheral origin of the aura was maintained until recent times, but with the discovery of the functions of the vessels and nerves, its seat was transferred to the latter; and the theory was held to be confirmed by cases to which far more significance was attached than their extreme rarity warranted, in which such local aura was associated with permanent lesion and irritation of a nerve in the part. It is now known, however, that the local aura is, in the vast majority of cases, merely the result of the commencing process in the brain, either affecting the consciousness directly, and causing a sensation which is referred to the part, or producing local spasm, and thus affecting the consciousness indirectly. That the aura is merely the commencement of the fit, and not its cause although not generally recognized until the present century, was pointed out three hundred years ago by Erastus.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

PEDIATRIC NEUROLOGY

This new department has been instituted to give more specific attention to the many neurologic diseases and conditions occurring among children.

DOUGLAS N. BUCHANAN, M.D., *Section Editor*

Electroencephalographic Studies of Infants and Children Who Acquired Intracranial Injuries at Birth

Odd Morstad, M.D. and Birge R. Kaada, M.D.

THERE are many studies of the location and pathologic characteristics in the nervous system of intracranial bleeding and asphyxia which proved fatal at birth. These have recently been reviewed by Ford.[4,5] The late effects of such injuries as were not fatal are more difficult to assess. These have been discussed by Hannes[8] and Schreiber[15] among others, and the most recent report is by Keith.[10]

This present investigation is an electroencephalographic study of 54 children who survived various degrees and types of natal intracranial injury. From the children delivered and cared for by the department of obstetrics and gynecology of the University Clinic at Oslo, 201 were first selected. They were chosen because all had a history of intracranial injury or asphyxia at birth or in the first six days of life. All were examined neurologically, their ages at the time varying from three to 21 years; 137 of the group were regarded as normal. The remaining 64 had either a history of repeated convulsions, evidence of mental retardation, a history of episodic attacks of rage, or pyramidal and extrapyramidal spasticity. It was finally possible to obtain electroencephalographic records of 54 children. In this group there were 11 who were normal and 43 who had neurologic abnormalities. The 54 were divided on clinical grounds into four groups (table 1):

1. Those with signs of severe intracranial bleeding at birth.
2. Those with less severe signs of a similar type.
3. Those with natal asphyxia.
4. Those in whom the signs of intracranial bleeding or asphyxia appeared some days after birth.

The electroencephalograph used in this study was an eight-channel Ediswan machine. The bipolar and average techniques of Goldman[6] and the coronal triangulation method of Gastaut[5] were used routinely. Records were some-

From the department of gynecology and obstetrics, University Clinic of Oslo (Rikshospitalet), and the department of neurology, Oslo City Hospital (Ullevaal), Norway.

TABLE 1.

Group 1. *Clinical signs of intracranial bleeding at birth.* (23 patients.)

	Number of patients	Electroencephalogram		
		Normal	*Focal*	*Generalized*
Convulsions with motor component	6	0	4	2
Mental retardation or periodic emotional disturbance as of rage	12	0	11	1
Pyramidal and extrapyramidal spasticity	3	0	2	1
Normal	2	2	0	0

Group 2. *Clinical signs suggestive of intracranial bleeding at birth.* (5 patients.)

Convulsions with motor component	2	1	1	0
Mental retardation or periodic emotional disturbance as of rage	1	0	0	1
Normal	2	2	0	0

Group 3. *Severe asphyxia at birth.* (18 patients.)

Convulsions with motor component	8	3	2	3
Mental retardation or periodic emotional disturbance as of rage	6	1	0	5
Normal	4	4	0	0

Group 4. *Signs of intracranial bleeding or aspyhxia appearing in the first week of life.* (8 patients.)

Convulsions with motor component	5	2	2	1
Normal	3	2	1	0

times taken from nasopharyngeal leads. The tracings were taken at the Oslo City Hospital, the department of neurology at University Clinic of Oslo, and at the psychiatric clinic, University of Oslo.

The details of the neurologic examinations of this whole group of 201 children have been reported.[10]

ELECTROENCEPHALOGRAPHIC RESULTS

1. Eleven of the 54 patients were regarded as normal, and of that group ten had normal electroencephalograms. The one abnormal tracing showed focal discharges.

2. There was a history of repeated major convulsions with motor components in 21 children. In six of this group the electroencephalogram was normal. In nine of the abnormal tracings there were focal discharges, and in the remaining six there were generalized and bilaterally synchronous 3 to 4 per second or 6 per second discharges. Figure 1 demonstrates characteristic portions of the nine tracings in which there were focal discharges. In eight there were random or rhythmic spikes or sharp waves of high amplitude and in one electroencephalogram a focus of random slow waves was recorded. In two electroencephalograms random and rhythmic 3 per second spike and slow wave complexes were recorded from the left parieto-occipital region. These discharges became more widely and more bilaterally distributed on hyperventilation. The abnormal discharges were frequently recorded from a wide area rather than from a sharply defined focus.

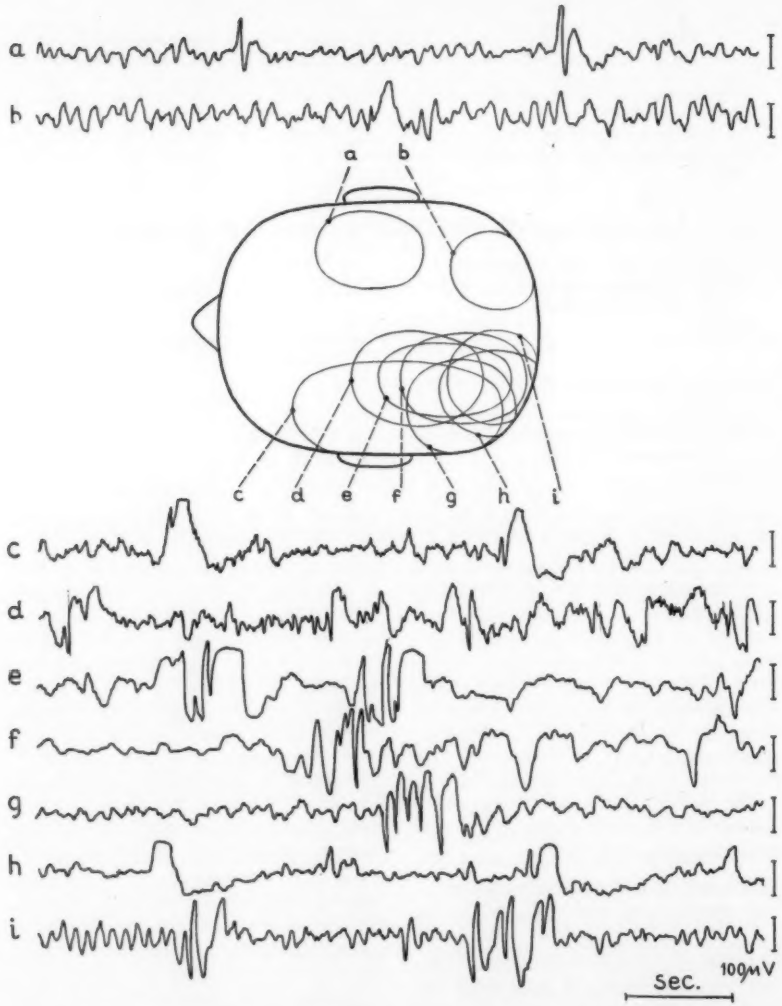

FIG. 1. *(above)* Portions of the E.E.G. records of nine children who had evidence of intracranial injury at birth and who later developed major convulsions. The areas outlined on the figure of the skull indicate the location of the focal abnormalities in each case.

FIG. 2. *(opposite page)* Portions of the E.E.G. records of 11 children who had evidence of intracranial injury at birth and who later developed mental retardation or erratic emotional behavior. The areas outlined on the figures of the skull indicate the location of the focal abnormalities in each case.

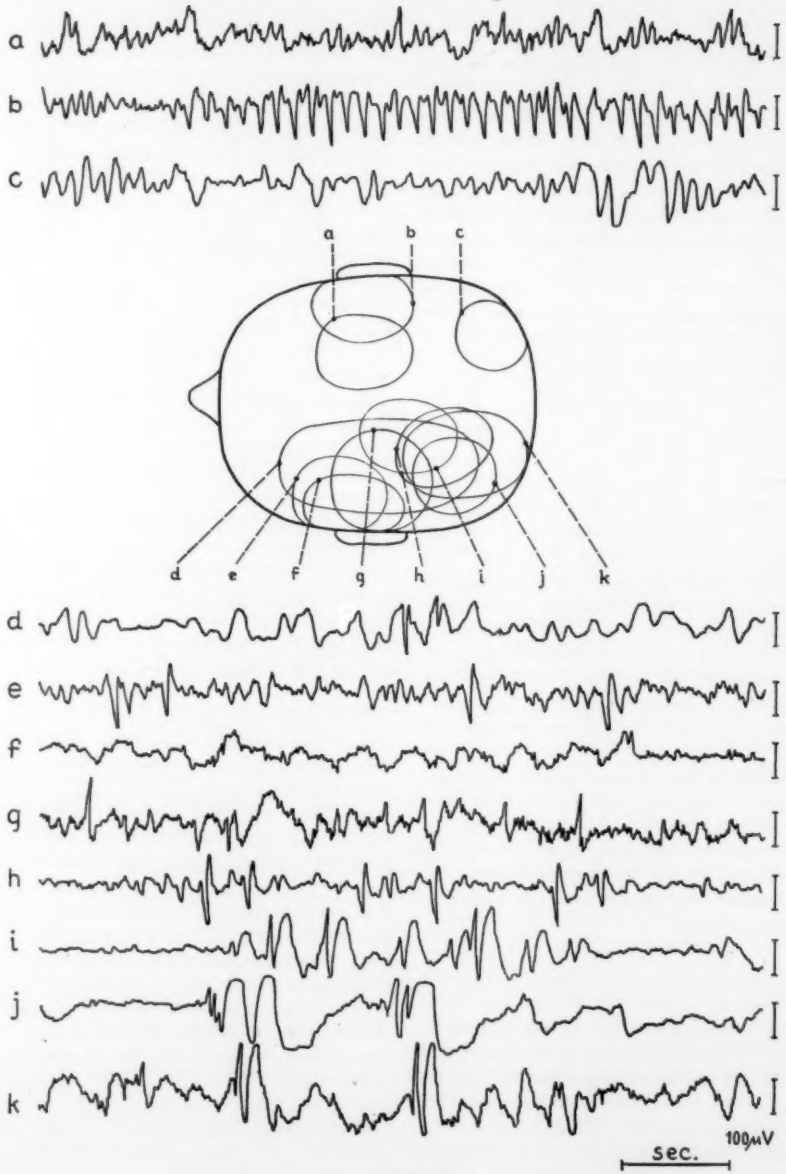

Figure 2.

3. Of the group of 19 who had a history of episodic attacks of rage or evidence of mental retardation only one had a normal tracing. Of the 18 abnormal records, 11 had focal abnormalities and in seven there were diffuse and bilaterally synchronous discharges. Characteristic portions of the 11 tracings which had focal characteristics are given in figure 2. The focal abnormalities in eight were random, high voltage spikes. In one there were 6 per second discharges and in two rhythmic, slow discharges. Mental retardation was present in ten of the 11 children who had these focal discharges. One child who had congenital dysphasia had a focus of spike discharges from the left temporal region and one who had alexia had slow wave discharges from the right frontoparietal region. In three children there were bilaterally synchronous discharges of 6 per second waves, with their maximum amplitude from the anterior temporal regions. In one child synchronous discharges from the frontal regions had the form of spikes, followed by 3 per second waves. In the electroencephalograms of two young adults there were long runs of 3 to 5 per second and 6 to 7 per second waves. Mental retardation was present in four of the patients who had bilaterally synchronous discharges. One child who had periodic attacks of rage had 6 per second discharges from both temporal regions and another had generalized 3 to 5 per second activity.

4. In three children who had a history of intracranial bleeding at birth there were signs of pyramidal and extrapyramidal spasticity. In the tracing of one child there was a focus of spike discharges in the right parieto-occipital region. In the second, high voltage spikes were found in the right posterior frontal and temporal regions. The electroencephalogram of the third child had a focus of 3 per second discharges over the left anterior lower temporal region.

COMMENT

There were 37 abnormal electroencephalograms in this study. A focal quality was present in 23 of these tracings. This incidence seems high. Figures 1 and 2 give the location of 20 of these foci and it is remarkable that only five are on the right side of the skull and 15 on the left. An attempt was made to correlate this left-sided emphasis with the type of delivery, but no relationship to the form of presentation could be established. Of the children who had evidence of injury to the left hemisphere, two were delivered by left occiput anterior presentation, seven by right occiput anterior, and one with a face presentation. In three children of this group outlet forceps were used and one child was delivered by cesarean section performed because of mechanical disproportion. Of these children who had injury in the right hemisphere, two were delivered by right occiput presentation, one by left occiput, one by breech, and one as a footling presentation. Outlet forceps were used in only one delivery.

In a study of the reaction to anoxia of various regions of the cat's brain made by Weinberger, Gibbon and Gibbon[14] they concluded that the cerebral cortex was more susceptible to anoxia than the other regions. They believed that with anoxia gross injury as well as less massive changes occurred first in the parieto-occipital and frontal cortex. They discovered indeed that if evidence of injury was not present in these two regions it was not found in other parts of the cortex. Courville[2] has stated that the calcarine region of the occipital cortex appears to be particularly sensitive to reduction of oxygen supply and this conclusion was reached in other studies where sudden cardiac arrest produced fatal anoxia.[3,8,9,11] These studies

may suggest why the areas of focal discharge pictured in figures 1 and 2 tend to lie in the region of the vertex and posterior portions of the hemispheres. As yet, however, there is no clue to the etiology of the left-sided preponderance of foci of discharge and no evidence that it is significant.

SUMMARY

1. A series of 54 children were studied by neurologic examination and by electroencephalogram.

2. All had a history of intracranial bleeding or asphyxia at birth.

3. Eleven of these children were normal.

4. Seventeen of the electroencephalograms were normal and 37 abnormal.

5. Twenty-three of the abnormal electroencephalograms had focal discharges.

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We have next to consider the disturbance of the higher cerebral faculties which sometimes attends the megrim paroxysm; this may be regarded for the most part as either intellectual or emotional. The former is represented in some instances by loss or impairment of memory, and in others by confused, incoherent, or tumultuous ideation, very rarely by hallucination; the latter by general mental depression, or vague subjective feelings of anxiety and dread.

Looking to the table of cases I see that these symptoms were present in one or other form in fifteen, or just a quarter of those entered. Both belong to the earlier stages of the paroxysm, and hence for the most part precede the headache. In some few cases, where the disorder is of the emotional kind, it may be delayed or prolonged to a later stage.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Neurology BOOK REVIEWS

The Founders of Neurology

Webb Haymaker, M.D., Editor. 1953. Springfield, Illinois: Charles C Thomas, Publisher. 479 pages, 133 illustrations, $10.50.

This is a most interesting collection of short biographical sketches of 133 neurologists, neuroanatomists, neuropathologists and neurosurgeons, whose work in the past has been of major importance in the development of our present day knowledge of the nervous system and its diseases. Written by 84 prominent living neurologists, and edited by Dr. Webb Haymaker with the collaboration and advice of many more, *The Founders of Neurology* is understandably an uneven book. The biographical sketches range from those of almost telegraphic brevity to a few biographies in which the richness of the prose seems inappropriate. In some instances, the inclusion of unnecessary bibliographic references tends to academic pretentiousness and does not contribute to either ease of reading or literary style. Probably included in an effort "to weave into the text, a running history of neurology" such citations neither add to the biographical interest nor do they, in any way, fulfill their function of presenting even the most abbreviated history of neurology.

Not a few readers will note errors of omission and commission in both the selection of men for inclusion in the book and the choice of biographer for those who are included. This is most understandable when the monumental character of the task is recalled, and it does not detract from the basic value of the collection but does add to the uneveness of the articles. It is impossible not to compare the present volume with *Neurological Biographies and Addresses* (1936, London, Oxford University Press), which was issued at the opening of the Montreal Neurological Institute. Such a comparison reminds one that biographic brevity and attempts at all-inclusiveness are usually achieved at some expense.

The format and illustrations are excellent. The collection of portraits alone makes the volume a valuable, historical repository. The book would be of most value if it could be used in conjunction with a true history of neurology. As it stands, it is a useful abbreviated biographical dictionary, but the flavor of a true biography is lacking. In no sense of the word is the book truly a history of neurology.

An interesting added feature of this book is the introductory section with short definitions of the European academic terms which are so often mystifying to those whose training and background is entirely American.

The Founders of Neurology is interesting and useful, but leaves the present reviewer unsatisfied and hopeful that a real history of neurology will soon be available.

A. L. D.

Disorders in Perception

Morris B. Bender, M.D. 1952. Springfield, Illinois: Charles C Thomas, Publisher. 110 pages. $3.00.

The obscuration or complete imperception and mislocalization of a sensory stimulus in one part of the body when another stimulus is applied simultaneously elsewhere has been known to clinicians for a long time. Yet the phenomenon never received the attention it deserves from the theoretical and practical points of view and so was never explored methodically. This clearly written little monograph summarizes the results of the assiduous observations of the phenomenon by the author extending over the past ten years and published in numerous articles which have aroused a considerable interest among neurologists.

The author calls the phenomenon of partial obscuration or complete imperception one of the two simultaneous stimuli as "extinction" and mislocalization of the stimulus from the part of the body where it was actually applied to another part as "displacement." The method of elicitation of these phenomena consists of three variants: (A) simultaneous stimulation of areas symmetrically situated on two sides of the body; (B) simultaneous stimulation of two dissymmetrically situated areas; (C) stimulation of two points situated on the same side of the body. Three different aspects of extinction and displacement are studied: the dominance of certain somatotopic sensory areas over the others; the incidence of imperception or displacement of one of the two simultaneous stimuli in normal individuals according to age (children and adults); the diagnostic correlation of the phenomena with the focal and diffused lesions of the central nervous system.

Normally there exists an orderly pattern of dominance of certain parts of the body over the others as follows: stimulus in the face area extinguishes the concurrent stimulus in any other part of the body, i. e., the face is dominant over all other parts; next in order of dominance are genital parts and upper trunk, hips and lower trunk, leg and foot follow in that order; the hand is, however, less dominant in regard to any other part of the body. The occurrence of the phenomenon of extinction or displacement of one of the two simultaneous stimuli is the more constant and the above pattern of dominance is the more consistent the younger is the group of children examined; the constancy of the extinction and displacement and consistency of the pattern of dominance decreases in normal adults; however, the extinction and dominance occur again frequently and consistently in adults with focal and diffused brain damage and are relatively more constant and more consistent in psychotic patients than in normal adults.

In an interesting graph the author summarizes the results of simultaneous hand-face stimulation as follows: on the initial test over 90 per cent of patients with organic mental syndrome, over 80 per cent of normal children from three to six years of age, about 75 per cent of adult schizophrenics, and 55 per cent of normal adults revealed extinction of hand stimulus and dominance of the face stimulus. However, in successive identical tests in the same individuals the incidences of extinction and constancy of face dominance over the hand fell off gradually on the tenth test to less than 5 per cent in normal adults and to about 10 per cent in schizophrenics, but only to slightly under 90 per cent in patients with organic mental syndrome and to about 80 per cent in children. These are challenging observations.

The practical implications of the phenomenon of extinction and of the method of simultaneous double stimulation emerges clearly in the clinical examination of sensory functions in the patients with focal and diffuse lesions of the brain, in hemiplegics, in patients with latent visual field defects and also in "sensory level" determination of lesions of the spinal cord. These practical aspects of the method of elicitation and observations of the disorders of perception are illustrated with brief summaries of the author's personal clinical case reports. The most interesting corollary of extinction is the phenomenon of *displacement* of a single or of one of the two simultaneous stimuli. According to the method of stimulation (A, B, C or single stimulus) and depending on the condition of the patient and also on the state of his perceptual "background," one may elicit the phenomenon of displacement in several general patterns: displacement from the point of actual stimulation to a symmetrically homologous point of the body across the midline, displacement towards a heterologous point usually in the more dominant area across the midline or to a dominant area on the same side of body and displacement into the extra-personal space. The method of simultaneous stimulation of heterologous points across the midline such as one side of the face and the opposite hand yield, as in the case of extinction, the most constant and consistent results; the mislocalization of stimulus occurs from the hand to face on the side of the hand, the patient reporting the sensation of both sides of face. The contralateral displacement is less common.

The author stresses the fact that the displacement occurs "across a gradient in sensation from an area of high to one of lower threshold of sensibility" usually in accordance with the pattern of somatotopic hierarchy of increasing manu-genito-axi-facial and distal-proximal dominance. He points out, however, that the elevation of threshold of perception is only one of many factors in perception which condition the extinction and displacement. Other factors, such as difference in intensity of stimuli, difference in timing of stimuli, type of sensory modality tested, difference between "stimulus figure" and "stimulus background," adaptation time, attention and like factors must be considered.

Thus far only the displacement of cutaneous modalities of stimuli have been explored, although preliminary studies indicate the occurrence of ipsilateral displacement in the vertical plane in half-field of vision. The author refers to the older literature in which contralateral displacement of single stimuli in tests of vision and of hearing have been reported. He described briefly other types of displacement such as allesthesia, synesthesia and exosomesthesia; the latter type – a displacement of a single or of one of the two simultaneous stimuli into extra-personal space, usually the object upon which the stimulated part (e. g., hand) rests, was seen to occur only in patients with a severe mental disorder.

The monograph is concluded with an instructive discussion of the current theories on extinction. A bibliography of 110 references and an index complete this interesting and informative little book. P.I.Y.

Neurology

Retroperitoneal Tumor as a Cause of Low Back and Leg Pain

G. W. Anderson, M.D. and Bernard J. Alpers, M.D.

RETROPERITONEAL TUMOR constitutes a rare and usually unrecognized cause of low back and leg pain. Its incidence as a cause of such pain is difficult to determine because of the lack of emphasis of the neurologic features of tumors in this location. Adequate attention has been devoted to other features of retroperitoneal tumors, but little emphasis has been placed on their neurologic symptoms. For this reason it has seemed desirable to report four cases in order to define the neurologic features by which tumors in the retroperitoneal space may be recognized.

REPORT OF CASES

Case 1. — A 63 year old man had a three week history of low back pain radiating into both lower quadrants and occasionally into the right leg. Examination revealed enlarged right kidney, hyperesthesia of the right leg and right lower back, and sluggish patellar and Achilles reflexes bilaterally. Laboratory studies showed 3+ albuminuria. Intravenous urography showed upward displacement of the right kidney. Operation and necropsy revealed a retroperitoneal lymphosarcoma.

History: The patient was a 63 year old white physician who was admitted to Jefferson Hospital on March 4, 1945, with a chief complaint of pain in the back. He was well until three weeks before admission when, while lifting a heavy log, he experienced a sharp sensation in his low back and had a severe, agonizing pain on his right side just below the costal cage. The sharp pain became a dull ache which was very severe on standing. It radiated around both sides into his groins and occasionally down the right leg for an

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undetermined distance. It was not increased by abdominal straining. The patient was most comfortable when lying flat; however, the pain never completely disappeared and he had difficulty sleeping because of it. At no time did he note impairment of movement of the leg nor evidence of sensory disturbances in his lower limbs. He had noted moderate weight loss and easy fatigability recently.

The past history revealed that the patient had had a ruptured appendix in 1917. He was a known diabetic for five years, controlled by insulin and diet, and had albuminuria for three years that was assumed to be due to an interstitial glomerulonephritis. One brother had posterolateral sclerosis.

Examination revealed enlargement of the right kidney; hyperesthesia of the right leg and lower right back; and sluggish patellar and Achilles reflexes bilaterally.

Laboratory data revealed a moderate anemia with 3,600,000 red blood cells per cu. mm. and 76 per cent hemoglobin. Urinalysis showed 3+ albumin and an occasional red and white blood cell. Blood sugar and urea and electrocardiogram were normal. Roentgenograms of the vertebrae and barium enema were normal. Intravenous urogram showed the right kidney pelvis to be displaced upward.

Course: The patient had an exploratory laparotomy on March 15, 1945 and a retroperitoneal tumor was encountered which, on histologic study, was found to be a lymphosarcoma. The postoperative course was stormy and the patient died on March 30, 1945. Autopsy revealed: 1) generalized fibrinopurulent peritonitis; 2) retroperitoneal lymphosarcoma; 3) old fibrous peritoneal adhesions with volvulus of the small intestine; 4) partial pulmonary atelectasis; 5) pulmonary congestion and edema; and 6) scattered fibrosed pleural adhesions.

Summary: The patient, a 63 year old man, developed moderately severe, sharp pain in the low back on attempting to lift a heavy log. The original sharp pain was replaced by a constant dull ache, aggravated by standing, and radiating into both groins and into the right leg. The right kidney was found to be enlarged on palpation and intravenous urography revealed upward displacement of the right kidney. Necropsy revealed a retroperitoneal lymphosarcoma.

The diagnosis in this instance was made on the basis of the physical and radiologic findings. The spread of pain into the groins gave rise to the suggestion that the seat of the trouble was retroperitoneal, an impression supported by the radiologic findings and confirmed by operation and necropsy.

Case 2.—A 36 year old man had a progressive history of right back pain and right lower quadrant pain of nine months' duration, occasional radiation of pain into the right testicle, with aching in the anterior and lateral aspects of the right thigh. Physical and neurologic examinations and routine laboratory studies were normal. Intravenous and retrograde urograms showed a lateral displacement of the upper third of the right ureter. Operation revealed a fibrosarcoma of the right psoas region.

History: The patient was a 36 year old white married physician who was admitted to Jefferson Hospital on December 17, 1950, with the chief complaint of pain in the back. He was well until March 1950, nine months before admission, when he began to experience dull, aching, intermittent pain in the right upper lumbar area radiating into the right flank to just above the umbilicus. The pain occurred about every other day lasting all day and was present for about six weeks, following which it disappeared. He then developed a constant dull aching in the low back associated with a distressing feeling in the right lower quadrant.

In September 1950, seven months after onset, the patient began to experience recurrence of the dull, aching, intermittent right upper lumbar pain with radiation of the pain around the right flank to just above the umbilicus. The dull pain became quite severe and steady. Intravenous urography revealed the upper portion of the right ureter to be displaced laterally. Further intravenous and retrograde urograms revealed lateral deviation

of the upper portion of the right ureter and also a constant defect at the right ureteropelvic junction without evidence of obstruction. Barium enema and roentgenograms of the upper gastrointestinal tract were normal.

The symptoms subsided during hospitalization over a period of five days, but about ten days after discharge from the hospital the patient had a recurrence of pain in the lower right back radiating into the right lower quadrant and at times into the right testicle. In addition he experienced an aching in the anterior and lateral aspects of the right thigh. The pain was aggravated by coughing, belching, and by using the foot brake in his car. It was not aggravated by recumbency. He had no urinary symptoms and no change in his sexual abilities or appetite. He had no weakness or paresthesias of the legs. Because of the persistence of his complaints he was readmitted to the Jefferson Hospital on December 26, 1950, for further evaluation.

The past history revealed a right eye injury when about ten years old, resulting in a traumatic cataract, and a duodenal ulcer of at least five years' duration, controlled by diet.

Examination revealed amblyopia of the right eye; a dilated right pupil fixed to light; external strabismus of the right eye; and absent patellar and Achilles reflexes bilaterally.

Laboratory data including complete blood count, urinalysis, blood urea, PSP and urea clearance tests were normal. Retrograde pyelogram revealed lateral displacement of the right kidney. The right psoas shadow showed abnormal bulging.

Course: The patient had an exploratory laparotomy on December 28, 1950 and a tumor mass involving the right psoas muscle was found. Biopsy revealed a fibrosarcoma. The patient was given supervoltage therapy after discharge from the hospital.

Summary: The problem in this instance concerned a 36 year old man with a progressive history of right back pain of nine months' duration, the pain radiating into the right groin and the right testicle and accompanied by an aching in the anterior and lateral aspects of the right thigh. Examination revealed nothing. The patient was suspected of having a retroperitoneal tumor but in spite of lateral deviation of the upper portion of the right ureter and upward displacement of the right kidney, the diagnosis was not made at the time of his original survey. Because of the persistence and progression of his complaints the urograms were repeated and revealed more lateral and upward displacement of the right ureter and right kidney and in addition a definite bulging of the right border of the psoas muscle. Operation revealed a retroperitoneal fibrosarcoma.

The diagnosis of retroperitoneal tumor with implication of the lumbosacral plexus was suspected on clinical grounds because of the history of radiation of the pain into the groin and testicle. It could not be definitely established however on clinical grounds alone, and in the last analysis the diagnosis in this instance was made by the radiologic findings which first revealed displacement of the ureter and subsequently showed progression of the defect.

Case 3.—A 32 year old woman had a history of right back and leg pain of 19 months' duration. Neurologic examination revealed moderate weakness and atrophy of the right lower extremity; absent right Achilles reflex; marked limitation of right straight-leg-raising test; saddle type sensory loss with extension down the left posterior thigh and lateral aspect of the right foot. Routine laboratory studies were normal. Barium enema and lumbar myelogram were normal. Radiologic evidence was seen of degenerative changes in the lumbosacral and sacroiliac regions and calcification in the right pelvis. Operation revealed a retroperitoneal fibrosarcoma.

History: The patient was a 32 year old white woman who was admitted to Jefferson Hospital on April 6, 1950, with the chief complaint of pain in the right back with radiation into the right leg of 16 months' duration. She was well until January 1949, 16 months prior to admission, when while pouring coffee she experienced discomfort in the right back described as a tired feeling, persisting constantly for three months until March 1949. In April 1949, one month later, the discomfort was replaced by pain which became gradually

worse so that by October 1949, ten months after onset of her complaints, she had quite severe, steady, aching pain in the right back. This was felt along the right lower back and right sacrum, into the anal region and sometimes even into the perineum. At the same time (October 1949), she began to experience pain in the right leg, beginning in the right buttock and extending along the back of the right thigh. It did not involve the right calf but it did involve the right heel. The pain was usually cramp-like but on occasion became very sharp. It was aggravated by walking, lying down and coughing. It was somewhat relieved by standing. Heat afforded very little relief. She obtained some relief from sedatives. In addition the patient had pins-and-needles sensation over the end of her spine and close to the rectum. She also occasionally noted a numb sensation in this area. The patient denied any urinary or fecal incontinence or any difficulty in starting her stream or constipation.

Examination revealed slight impairment of the lumbar curve; some limitation of forward bending; slight spasm of the paravertebral muscles on the right side; tenderness in the right sciatic notch; positive Lasegue and straight-leg-raising tests on the right side.

Laboratory data including complete blood count, urinalysis, stool and blood Wassermann and Kahn examinations were normal. Spinal fluid examination was negative except for 54 mg. per cent protein. Roentgenograms of the chest, barium enema and lumbar myelogram were normal. Those of the lumbosacral area and pelvis showed minimal degenerative changes.

Course: The patient was discharged on April 14, 1950 on a regime of sedation, diathermy and antispasmodics as a case of back and leg pain due to sacroiliac arthritis. She continued to have increasingly severe right back and leg pain and in July 1950, 18 months after the onset of her complaints, she developed numbness in her left leg and right foot. At that time the patient was examined at another hospital and neurologic examination revealed a saddle type of sensory loss with extension down the left posterior thigh and lateral aspect of the right foot; moderate weakness and atrophy of the right lower limb; absent right Achilles reflex; marked limitation of right straight-leg-raising test and some limitation of left straight-leg-raising test. Roentgenograms of the lumbosacral spines at this time revealed a partially calcified tumor mass eroding particularly the right side of the sacrum in the vicinity of the second and third sacral segments. The patient was operated on August 3, 1950, and a tumor mass was disclosed in the retroperitoneal space which on histologic examination was found to be a fibrosarcoma. The coccyx and four lower sacral segments were removed as well as the right sciatic nerve sheath and portions of the right sacroiliac joint and right ilium. The patient did well postoperatively but because of recurrence of her symptoms and a defect by myelogram at the lumbosacral junction she was re-explored on December 13, 1950, and it was noted that the tumor involved the cauda equina, the rectum and the sacroiliac joints. In January 1951 the patient had a prefrontal lobotomy because of extreme pain and a profound depression with suicidal tendencies.

Summary: This case involved a 32 year old white woman with a progressive history of 19 months' duration of right back and leg pain, who 16 months after onset of symptoms revealed very little on examination. She was suspected of having involvement of the roots of the right sciatic nerve by an intervertebral disc, but Pantopaque myelography was normal. Routine roentgenograms of the lumbosacral vertebrae and pelvis showed evidence of degenerative changes in the lumbosacral and sacroiliac articulations and her pain was originally attributed to these sources. Progression of her symptoms and signs led to further examination at another institution, and roentgenographic evidence of a calcifying, eroding tumor in the region of the right sacrum was found.

The diagnosis in this case was made by roentgenograms which revealed evidence of erosion of the right side of the sacrum. This was not observed in her original survey, though a later review of the films revealed the changes which would have established the

diagnosis. There were few findings referable to the nervous system at the time of her original survey, but these would have been of little consequence if the roentgenographic films had been interpreted properly. By the time the patient returned from a subsequent survey there was clear evidence of involvement of the lumbosacral plexus and the radiologic findings were of less significance, though they constituted important corroboratory evidence. In the last analysis the diagnosis must be regarded as having been demonstrated by roentgenogram, though the findings were not recognized at the time of the original examination.

Case 4.—A 54 year old man had a six months history of right lower back pain radiating into the lateral aspect of the right thigh and calf and extending into the toes of the right foot. Examination revealed a firm, non-tender, indurated area along the right inguinal ligament; a right testis two times larger than normal; an edematous right scrotal sac; 2+ pitting edema of the right leg; slight atrophy of the right gastrocnemius muscle; slight limitation of right straight-leg-raising test; decreased right patellar and absent right Achilles reflexes. Routine laboratory studies were normal. Roentgenograms of the chest, lumbar myelogram and barium enema were normal. Intravenous urography showed no evidence of concentration of dye in the right kidney. Laparotomy revealed a grade 3 epidermoid carcinoma obstructing the right ureter and invading the right psoas muscle.

History: The patient was a 54 year old white man who was admitted to the Pennsylvania Hospital on December 4, 1951, with a chief complaint of back and right leg pain of five months' duration. He was well until June 1951, six months before entrance, at which time he began to feel constant, sometimes sharp, shooting pain in the right lower back radiating into the lateral aspect of the right thigh and calf and extending into the toes of his right foot. The pain in these regions was aggravated by lying on his back and sometimes by walking. It was not affected by coughing or straining. Occasionally, especially in the month prior to entrance, the pain had radiated into the right groin and over the lower portion of his right abdomen. In addition, the patient sometimes felt a tingling sensation in the right testicle. Codeine and aspirin for the pain gave little relief.

In addition to pain, the patient had an accompanying numbness in the toes of the right foot which had been constant for the past five months, sometimes more intense than others. The patient had also noted a slowly progressive, painless swelling of the right scrotum and right leg. He had on several occasions noted that he was unable to pass urine, though he had a definite desire to void. He had constipation requiring a laxative every other night to insure daily bowel movements since the onset of the pain. He had noted a 20 pound weight loss in four months. There were no other significant symptoms. The past history revealed that eight or nine years previously while turning a fly wheel it suddenly started and he lurched forward with the occurrence of sudden low back pain that made it difficult for him to straighten up. This back pain persisted for one week and subsided.

Examination revealed a firm, non-tender, indurated area which extended along the right inguinal ligament; enlargement of the right testis to twice its normal size, globular in shape and rather flabby to palpation; an edematous right scrotum which contained an excess quantity of fluid; 2+ pitting edema of his right leg; atrophy of the right gastrocnemius muscle; slight limitation of straight-leg-raising on the right; decreased right patellar and absent right Achilles reflexes.

Laboratory data showed the blood count, urinalysis and spinal fluid examinations to be normal. Roentgenograms of the chest, lumbar myelogram and barium enema were normal. Intravenous urography showed no concentration of dye in the right kidney. Right retrograde pyelography was attempted but all attempts at ureteral catheterization met a complete obstruction at 3 cm.; however, phenolsulfonphthalein was obtained from the right ureter.

Course: The patient continued to complain of quite severe pain in his lower right back and right leg in spite of quite heavy doses of narcotics. An exploratory laparotomy was

TABLE 1

REPORTED CASES OF RETROPERITONEAL TUMOR WITH NEUROLOGIC SYMPTOMS

Author	*Age*	*Sex*	*Distribution of Pain*	*Duration*	*Physical Examination*	*Neurologic Examination*	*X-ray Findings*	*Histologic Diagnosis*
Sweetser[11] (1942)	60 yrs.	M	Right lumbar region, inner aspect of right thigh and leg.	3 mos..				Adenocarcinoma of ascending colon
Mentzer[15] (1944)	48	M	Left rectum, left buttock and posterior aspect of left thigh and leg to heel.	Not recorded	Masses in ischiorectal space.	Negative		Neuromyxo-fibrosarcoma
Case Records of Mass. Gen. Hosp. Case 34311[7] (1948)	75	M	Lower right thigh, back and right flank.	6 yrs.	Superficial and deep tenderness over anterior aspect of right thigh.	Negative	Positive I. V. urogram	Fibrosarcoma
Anderson and Alpers (Case 1)	63	M	Low back pain with radiation into both groins and down right thigh.	3 wks.	Palpably enlarged right kidney.	Hyperesthesia of right lower back and right leg.	Positive I. V. urogram	Lymphosarcoma
Anderson and Alpers (Case 2)	36	M	Right flank, right lower quadrant, right testicle, and anterolateral aspect of right thigh.	9 mos.	Negative	Negative	Positive I. V. and retrograde urograms	Fibrosarcoma
Anderson and Alpers (Case 3)	32	F	Right lower back, sacrum, anal region and perineum, right buttock, right posterior thigh and right heel.	19 mos.		Lumbar curve straightened, limitation of forward bending, paravertebral muscle spasm on right, tenderness in right sciatic notch, positive Lasegue and straight-leg-raising tests.	Positive pelvis x-rays	Fibrosarcoma
Anderson and Alpers (Case 4)	54	M	Right lower back, right lower quadrant, lateral aspect of right thigh, calf and foot, right testicle.	5 mos.	Indurated mass in right lower quadrant, enlarged right testis, edematous right scrotum, 2+ edema of right leg.	Atrophy of right gastrocnemius muscle, decreased right patellar and absent right Achilles reflexes.	Positive I. V. urogram	Grade 3 epidermoid carcinoma of right ureter

performed on December 19, 1951, and revealed a marked hydronephrosis and right hydroureter with a tumor mass involving the ureter at the level of the pelvic brim, and invading the right psoas muscle. The right kidney and ureter were removed and a biopsy taken from the infiltrated psoas muscle revealed a grade 3 epidermoid carcinoma of the right ureter with invasion of the right psoas muscle. The patient recovered and was discharged on December 30, 1951.

Summary: The patient was a 54 year old white man with a progressive six month history of right lower back pain and right leg pain. Examination revealed a mass in the right lower quadrant causing obstruction of lymph drainage from the right lower extremity and right scrotal sac. He also had evidence of involvement of the right lumbosacral plexus. He was suspected of having a retroperitoneal tumor and intravenous urography showed no dye concentrating in the right kidney. Attempted retrograde pyelography met obstruction in the right ureter. Operation revealed a grade 3 epidermoid carcinoma obstructing the right ureter and invading the right psoas muscle.

The diagnosis in this instance was made on the basis of clinical findings consisting of leg pain with radiation into the groin and testicle, and evidence on examination of lumbosacral plexus involvement. Because of spread of the pain beyond the limits of the sciatic distribution, the absence of the patellar reflex and the evidence of testicular and scrotal swelling, the clinical diagnosis of lumbosacral plexus involvement due to retroperitoneal tumor, further studies to establish the diagnosis were carried out. These led to a diagnosis of retroperitoneal tumor involving the right psoas muscle and extending into the right lumbosacral plexus.

REVIEW OF REPORTED CASES

The majority of the reported cases have been concerned with the systemic features of retroperitoneal tumors. This is easy to understand in view of the fact that tumors in the retroperitoneal region cause symptoms referable to other organs in most instances. Neurologic symptoms appear in some cases and may in fact be the first indications of a retroperitoneal tumor. A few instances have been recorded in which the neurologic symptoms dominated the clinical features of the problem. Doubtless, there are others, but it is difficult to find them in the large number of cases reported in the literature, since emphasis has been on other symptoms.

About 500 cases of primary retroperitoneal tumor had been reported up to 1946.[1] Since then 74 cases have been reported also in the English literature.[2–7] The usual symptoms of such tumors consist of vague digestive disturbances, progressive weight loss, weakness, constipation, urinary frequency and urgency, and complaints of abdominal swelling.[1,3,8–14] Less common are indefinite pain in the lower abdominal quadrants;[1,7,9] edema of the lower limbs;[1,3,6,12,13] weakness with muscular atrophy of the leg;[2] difference in surface temperature of the extremities;[1,6,12,13] and back and accompanying leg pain[7,11,13,15] (table 1).

CASES WITH NEUROLOGIC SYMPTOMS

Judging by the recorded cases of retroperitoneal tumor, back and leg pain are infrequent manifestations of this condition. The reported case records of the Massachusetts General Hospital[7] (case 34311) refers to a 75 year old man who was admitted to the hospital with the complaint of pain in the right flank. Six years before admission he developed superficial pain in the right lower

thigh. Two months later he noticed a sudden weakness of the right leg and at the same time became aware of the fact that standing caused severe pain in the back and right leg. Two months before admission he had occasional mild right flank pain, which later became persistent and occasionally radiated into the right lower quadrant. Examination revealed superficial and deep tenderness on the anterior aspect of the right thigh. Roentgenograms of the spine were normal. Intravenous urogram revealed no dye excretion from the right kidney . A retrograde urogram was unsuccessful. Operation and later necropsy revealed a retroperitoneal fibrosarcoma with pressure on the right kidney, extension to the inferior vena cava, duodenum and ascending colon, and lung metastasis.

Mentzer[15] reports the case of a 48 year old white man with a history of pain in the left side of the rectum radiating into the left buttock and down the back of the left thigh and calf to the heel. The pain increased gradually in severity, was worse when sitting, and was somewhat relieved by standing. Examination revealed irregular, rounded, hard masses in the skin between the anus and ischium. Masses were felt also through the left rectal wall, pressure on them causing radiating pain into the left heel. Operation revealed masses in the ischiorectal space with a large mass compressing the left sciatic nerve. This proved to be a neuromyxofibrosarcoma on histological examination.

Sweetser[11] reported the case of a 60 year old man with a three month history of pain in the right lumbar area, radiating into the inner side of the right thigh and leg. It was reported to be made worse by movement and was associated with dysuria and nocturia. Operation revealed an adenocarcinoma arising from the colon.

There have undoubtedly been other cases reported with neurologic symptoms, but it is difficult to extract them from the recorded instances of retroperitoneal tumor since they were incidental in the course of the disease. In relatively few instances have the neurologic symptoms apparently been sufficiently striking in themselves to lead to a diagnosis of tumor in the retroperitoneal space.

NEUROLOGIC CHARACTERISTICS OF RETROPERITONEAL TUMOR

In the four cases here recorded the duration of symptoms varied from three weeks to 19 months. All were characterized by constant low back pain in the lumbar area, described usually as dull and aching in quality, but becoming severe and agonizing at times. In all instances the pain was aggravated by movement. In two cases it was increased on recumbency, but in the other two cases it was not affected by lying down. In two of the cases the back pain was increased on straining by coughing, sneezing or bowel movement; in one case these had no effect on the pain and in the fourth case no data were available regarding these maneuvers.

In all instances the back pain was associated with pain in the leg. In two instances the back and leg pain appeared simultaneously; in two cases the

leg pain appeared eight and ten months after the onset of back pain. The radiation of the leg pain failed to follow constant channels and was reported in the lateral and anterior aspects of the thigh, the lateral aspect of the right thigh and calf and the foot, and the posterior aspect of the thigh and calf. Bilateral lower abdominal pain was felt in one instance, and two of the three males had unilateral testicular pain. One of the patients had edema of the painful lower limb as well as of the scrotal sac, and one patient had a constant numbness of the toes. Examination revealed an enlarged kidney in one case and an indurated mass in the groin with accompanying edema of the lower limb in another.

Neurologic examination revealed leg weakness with atrophy but without fasciculations in two cases; decreased leg reflexes in the lower limbs in four cases; and sensory changes in two cases. Limitation of movement of the painful limb was present in Lasegue and straight-leg-raising tests in two cases. In only one case was the routine roentgenogram helpful, revealing destruction of the bones of the pelvis. In three instances intravenous urogram revealed evidence of a tumor. Pantopaque myelograms in two instances were normal and spinal fluid examination was also normal in two cases.

DIAGNOSIS OF RETROPERITONEAL TUMOR

The diagnosis of retroperitoneal tumor is ordinarily made on features other than neurologic, but there are instances in which neurologic symptoms predominate either as late or early manifestations of the disease. The crucial problem, apart from early recognition, consists of separation of tumors in the retroperitoneal space from other conditions which cause low back and leg pain. They are characterized primarily by pain in these areas, and like other conditions causing pain in the back and leg, back pain may be present alone before leg pain develops. The condition cannot be recognized on the basis of low back and leg pain alone unless there are other evidences of retroperitoneal tumor, or unless the leg pain is distributed in the anterior thigh region, in contrast to the posterior thigh pain of a typical sciatic problem. In only one of our cases, however, was the pain in the anterior thigh and typical sciatic pain was present in another. Hence anterior thigh pain is not a constant finding. The possibility of retroperitoneal tumor as a cause of back and leg pain must be given serious consideration, however, if pain is described at the same time in the lower abdomen, the groin, testicle, penis, vagina or rectum. Radiation of pain into the genitals requires consideration of implication of the lumbosacral plexus and must give rise to the possibility of a retroperitoneal tumor as a cause of the pain. Further consideration of a retroperitoneal mass follows if there is a history of swelling of the limbs or scrotum. Apart from the history of distribution of the pain, there is nothing in the neurologic examination which confirms the diagnosis. However, if physical examination reveals evidence of a mass in the abdomen, the diagnosis of a retroperitoneal tumor can be established with relative certainty, provided the usual symptoms of a retroperitoneal tumor are present — vague digestive

disturbances, progressive weight loss, weakness, constipation, urinary frequency and urgency and abdominal swelling. Routine laboratory procedures are of little help unless evidence is found on roentgenographic examination of a bony lesion. The most useful laboratory procedure, however, if retroperitoneal tumor is suspected, is either intravenous or retrograde urogram, which in three of our cases revealed evidence of tumor.

The recognition of retroperitoneal tumors as a cause of low back and leg pain has its practical significance. It enables a separation of the cases in question from cases of herniated intervertebral disc and other causes of leg pain and may at times lead to an early diagnosis of retroperitoneal tumor.

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Megrim has been supposed to be pre-eminently a one-sided affection, but we have already shown that, if we adopt a natural rather than an artificial definition of it, this feature can no longer be regarded as constant or essential. Nevertheless, a not inconsiderable proportion of cases are one-sided, and as this is a character which belongs alike to several of the phenomena it will be well to consider it here.

So far as the headache is concerned, I find by reference to the analysis of cases only 17 entered as unilateral, and 7 as imperfectly unilateral, or sometimes unilateral and sometimes bilateral, against 34 bilateral cases. I am inclined to think, however, that if more exact inquiries had been made, many of the bilateral cases would have proved to be very unequally so, and to belong rather to the former category.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders*, published in 1873.

Observations on Pentosuria in Neuromuscular Disorders

A. L. Drew, M.D. and B. T. Selving, B.S.

IT HAS BEEN REPORTED[1] that the urine of patients with muscular dystrophy contains a pentose sugar, d-ribose, excreted as a phosphorus-containing complex. Later Orr and Minot[2] suggested that the detection of ribose might serve as "a clinical test for muscular dystrophy."

Because of the potential importance of these observations, preliminary investigations along similar lines were carried out. Although occasional difficulty is encountered in establishing the diagnosis of muscular dystrophy, the major importance of this observation is not in its application as a diagnostic test, but lies in its potential etiologic significance. It is possible that, by future quantitation, an objective index of therapeutic efficacy of various methods of treatment might be developed.

Certain inconsistencies and discrepancies have been observed. These do not, perhaps, detract from the diagnostic significance of "d-ribosuria," but they do make the application of the observations to etiologic studies open to some doubt. In addition, there is a body of literature concerning pentosuria which should be considered in evaluating reports of pentosuria in specific disease entities.

METHOD

For the most part the first morning urine was collected from hospitalized patients who had been on a fruit-free diet for 24 to 48 hours. Because of the observation made by Minot et al.,[2] "aging" of samples was permitted. Most tests were carried out on urines preserved with thymol and kept from several days to several weeks. All specimens were subjected to a 45 minute qualitative Benedict's test (8 to 10 drops of urine and 5 cc. of Benedict's solution heated 45 minutes in a boiling water bath). At this point our procedure deviates from that outlined by Orr and Minot[2] in that, contrary to their procedure, all specimens, even though negative, were carried through the next steps.

In order to remove interfering substances, the urine is treated with freshly washed yeast (30 to 40 cc. of urine was mixed with half this volume of 40

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per cent suspension of washed yeast and allowed to stand at room temperature for 15 minutes – the mixture was occasionally stirred). This procedure results in the removal of the fermentable sugar. The further removal of interfering substances is accommplished by treatment with Lloyd's reagent (1.5 gm. of Lloyd's reagent is added for each 10 cc. of original urine). This treatment will remove creatinine, creatine and uric acid. It should be noted that glycuronates* and polyphenols are not removed with the two procedures. Benedict and Osterberg[3] described a method of treating urine with mercuric nitrate which resulted in the removal of glycuronates and polyphenols. Minot et al.[1] noted this step, but apparently did not incorporate it in their routine procedure. Because of the difficulty in distinguishing the osazone of glycuronic acid from that of the pentose sugars,[4–6] we have considered treatment of the urine with mercuric nitrate an integral part of the procedure.

After treatment with mercuric nitrate the sample is again subjected to a 45 minute Benedict's test. The final step is the preparation of the osazone with phenylhydrazine according to the procedure described by Orr and Minot.[2]

RESULTS

The urine of 31 patients was examined. The detailed findings are tabulated below.

TABLE 1

Diagnosis	*Number of cases*	*Number yielding osazone crystals*
Muscular dystrophy	4	4
Myotonia dystrophica	3	3
Myotonia congenita	3	3
Progressive spinal atrophy	2	0
Amyotrophic lateral sclerosis	1	0
Guillain-Barré syndrome	1	0
Diabetic neuropathy	1	0
Primary amyloidosis	1	0
Multiple sclerosis	2	1
Convulsive disorder	2	1
Migraine	1	0
Dermatomyositis	1	1
Postherpetic neuralgia	1	0
Normal (fruit-free diet)	2	0
Normal (heavy fruit diet)	1	1
Cerebral palsy	1	1
Piamedullary angioma	1	1
Neurofibroma of dorsal root	1	1
Klippel-Feil syndrome	1	1
Scalenus anticus	1	1

*The older term, "glycuronates," is used in the sense of "glucuronates and/or uronates" of the more modern terminology.

The ten cases of undoubted dystrophy, myotonia dystrophica, and myotonia congenita yielded osazone crystals in all respects identical to those described as characteristic of pentosazones.

Pentose could not be found in the urine of patients exhibiting marked muscle wasting, in cases of progressive spinal atrophy, amyotrophic lateral sclerosis, and the Guillain-Barré syndrome.

In addition to these expected results, characteristic osazone crystals were isolated from the urine of seven patients whose disease was in no way related to either muscle wasting or a dystrophic syndrome. The finding of pentose in the urine of the single case of dermatomyositis is less readily classified as a false positive since this particular entity has some "dystrophic" features.

The ready production of pentosuria in a normal individual as a result of heavy fruit intake is best classified as a case of alimentary pentosuria. This view is confirmed by the fact that several specimens from the same individual were normal when he was placed on a fruit-free diet.

A total of 13 urines failed to reduce Benedict's solution after treatment with yeast, Lloyd's reagent, and mercuric nitrate. These same specimens did yield definitely detectable and identifiable osazone crystals with characteristics indistinguishable from those obtained from a test solution of d-ribose. Further, test solutions of 0.5 per cent d-ribose failed to reduce Benedict's solution after treatment with yeast, Lloyd's reagent, and mercuric nitrate, but did yield a relatively heavy crop of osazone crystals. Similar results were obtained when the mercuric nitrate treatment was omitted. In this group of 13 specimens there were four urines from muscular dystrophy cases, two urines from myotonia dystrophica patients, and the urine of two cases of myotonia congenita.

DISCUSSION

In a relatively small series of cases the presence of pentosuria in the urine of cases of muscular dystrophy, as originally reported by Minot et al.[1] and Orr and Minot[2] has been confirmed. A limited number of observations on the urine of patients exhibiting marked to moderate degrees of muscular atrophy also confirmed the observations of the previous workers. There was no evidence of pentosuria in conditions associated with muscular atrophy.

By carrying the urine specimens through all steps, a possible source of error in the technique is detected. Orr and Minot[2] state that "... the absence of reduction at this point (the second 45 minute Benedict's test) indicates that they (the free pentoses and complexes of interest) are not present in detectable amounts." On the basis of the results indicated above, failure to obtain reduction of Benedict's solution following treatment with yeast, Lloyd's reagent, mercuric nitrate, does not necessarily exclude the presence of an osazone former in the urine specimen. In a limited number of patients suffering from muscular dystrophy, test solutions of d-ribose and some false positive urines of patients who did not exhibit dystrophic syndromes, it was found that, despite the negative Benedict reduction after treatment with yeast,

Lloyd's reagent and mercuric nitrate, a characteristic osazone could be detected with application of the phenylhydrazine test. These results strongly suggest that the Benedict's test is not a sufficiently sensitive screening technique, and that, unless in all cases the formation of an osazone is attempted, the absence of a pentose sugar cannot be assumed.

Minot and her coworkers,[1,2] on the basis of their observations, conclude that the "presence of ribose is due to a specific error of cell metabolism, possibly not confined to the muscular dystrophies, but universally present in them." In this study pentosuria was demonstrated in every case of muscular dystrophy and related disorders. However, in a number of instances a positive phenylhydrazine test with the production of characteristic osazone crystals was noted in individuals exhibiting clinical entities totally unrelated to the dystrophies. These "false positives" were re-examined with entirely new reagents, and identical results were always obtained. It must be admitted that alimentary pentosuria cannot be excluded entirely, although these patients had been placed on a fruit-free diet, and, to the best of our knowledge, remained on this diet during the testing period.

The problem of pentosuria in conditions other than the muscular dystrophies is a large and somewhat confused one. There are some differences of opinion as to the existence of alimentary pentosuria. Rangier and de Traverse[7,8] have stated that pentosuria can only occur as a metabolic error. Johnstone[9] was able to demonstrate pentosuria in 89 per cent of a series of patients who drank 1½ liters of apple juice. In our experience we have been able to produce alimentary pentosuria at will in at least one otherwise normal individual. In this person a casual specimen proved to be positive for pentose. The individual was then placed on a fruit-free diet and no pentose was obtained from the urine. Later a heavy fruit diet was instituted and again pentose was recovered.

Perhaps more important than the question of alimentary pentosuria is the definite possibility of pentosuria occurring from toxic causes and as an acquired metabolic error. Johnstone[9] noted that morphine appeared to facilitate the production of pentosuria in his series. Margolis[10] has classified chronic pentosuria as acquired, toxic and inborn. He reports pentosuria following the administration of morphine, Pantopon and amidopyrine. He also found pentosuria associated with migraine, as well as in some nine other miscellaneous cases of "acquired chronic pentosuria," and stated that the condition is "apparently brought on and aggravated by infections, nervous trauma, and other toxic environmental factors." He was also struck by its apparent link with migraine and a so-called vagotonic constitution, and stated that in "a few instances it has behaved clinically as other allergic diseases." Protas[11] has reviewed and evaluated the work of Margolis and others on the subject and indicates that pentosuria may be a chronic acquired condition without specific metabolic implication. The transient occurrence of pentosuria in the acute febrile state of poliomyelitis was noted by Orr and Minot.[1]

Surprisingly little is known concerning the basic metabolism of ribose.

Scott and Cohen,[12] in reviewing the subject, felt that there were three possible routes of pentose formation. One of these is by decarboxylation of the corresponding uronic acid. However, the corresponding uronic acid of d-ribose has not been shown to occur naturally. The second method of ribose formation is by the enzymatic condensation of smaller fragments as is implied by the possible reversal of the cleavage of ribose-5-phosphate to form triose phosphate. Sable[13] has described an enzyme (ribokinase) which is apparently capable of facilitating this reaction. The third method of formation is the oxidative change from glucose phosphate by way of glucose-6-phosphate dehydragenase. Further oxidation of this system may yield ribose-5-phosphate. The fact that ribokinase may catalyze the transfer of phosphate from adenosine triphosphate to ribose is of some interest, clinically, in view of the recent report of Persson[14] who reported some clinical improvement in five cases of dystrophy treated with adenosine triphosphate. This clinical change was paralleled by an alteration in creatine, creatinine, and phosphate excretions. He did not make any study of ribose excretion in these patients.

Reference to the literature[4–6] indicates that it is very difficult to distinguish the osazone of glycuronate acids from the osazone of the pentose sugars. In addition, Everett and Sheppard[15] state that phenyl-semi-carbazide formed from urea, yields an osazone similar to that under consideration, and Patterson[16] reports the presence of an unidentified osazone forming substance in normal urine after treatment with yeast and mercuric nitrate. These possible sources of error have not been investigated, but raise the question of the final positive identification of the abnormal substance as a pentose, or more specifically, as d-ribose.

SUMMARY AND CONCLUSIONS

In a small series of cases pentosuria was demonstrated in cases of muscular dystrophy, myotonia dystrophica and myotonia congenita.

Pentosuria was not observed in cases of muscular atrophy.

Evidence is brought forward to suggest that the technique of screening with the Benedict's test is not sufficiently sensitive, and that formation of the osazone should be attempted in all cases.

Conditions other than muscular dystrophy may be associated with pentosuria. Alimentary pentosuria, acute and chronic acquired pentosuria, and less common cases of congenital pentosuria must be distinguished.

It is suggested that quantitative ribose studies might be of some value in following the course of muscular dystrophy patients and that considerable caution should be exercised in the interpretation of ribosuria until more basic biochemical data are available.

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The aura of an attack, using the term in its widest meaning, as signifying the subjective commencement, may consist in a consciousness of motion, or of sensation, or in a mental state. It has been long and often maintained by Hughlings Jackson, in extension of the older view of Laycock, that the whole brain is made up of structures which subserve sensori-motor processes, and that into such processes all its functions may be resolved. It is unnecessary now to consider this view as a whole, but that every structure of the brain concerned with sensation proper is connected, directly or indirectly, with a part concerned with motion, may be regarded as a proposition scarcely needing proof. A discharge, such as occurs in an epileptic fit, taking place in either of these related structures, may remain confined to that in which it commenced, but it usually leads to a discharge in the other. The two may act so simultaneously that the resulting motion and sensation occur together. The patient may feel a tingling in his hand at the same moment as the fingers begin to twitch. Or the discharge in one may lead the way – be followed by the other at an interval. The twitching or the tingling may come first. I think that it is of importance to determine, in any given case, with which the attack commences – the motion or the sensation – i. e., whether the motor or the sensory centre leads in the discharge. By so doing we are able to understand better the association of aurae and their progress. It is necessary, however, carefully to discriminate the form of the sensation, because, as Hughlings Jackson has also pointed out, the consciousness may be affected directly by the action of a motor centre, although no movement results. There are motor sensations as well as sensory sensations, and, as we shall see, a fit may begin by a sense of motion before any actual movement occurs, and the sensation of motion may be vastly in excess of the real movement. The word "sensation," however, will here be used, when unqualified, to signify a sensation proper, such as numbness, tingling, and the like.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Metabolism of Copper in Hepatolenticular Degeneration

Walter T. Zimdahl, M.D., Irving Hyman, M.D. and Edward D. Cook, M.D.

THE disease now generally known as hepatolenticular degeneration described by Wilson[1] in his paper on progressive lenticular degeneration has since engaged the attention of many investigators. Early reports of abnormal accumulation of tissue copper and of an excess of this element in the urine has been confirmed by Cummings[2] and Denny-Brown.[3] Cummings claimed that clinical improvement occurred in patients treated with injections of 2,3-dimercaptopropanol (BAL) which further inrceased the urinary excretion of the copper. An increased urinary excretion of aminoacids in the absence of hepatic failure was first reported by Uzman and Denny-Brown in 1948.[4] This increase has since been shown to be due to a renal defect and to be unassociated with any excess of aminoacids in the plasma.[5,6]

The present paper is concerned with further investigation of abnormal copper metabolism in patients with hepatolenticular degeneration (Wilson's disease). Serum copper levels of such patients tend to be elevated, and the urinary levels of copper tend to be far in excess of normal daily excretion figures. The normal range of serum copper has been established to be between 86 and 161 microgms. per 100 ml.[7] Estimations in normal subjects have all given values within this range, but in two cases of hepatic cirrhosis, levels of 190 and 270 microgms. were found by Matthews et al.[8] Estimation of urine copper excretion per 24 hours by Matthews in 17 normal adult subjects gave values ranging from 10 to 68 microgms. per 24 hours with a mean of 35. In two patients with Wilson's disease, the excretion showed a mean of 864 and 625, respectively. Porter[9] found the copper excretion in the urine of 11 normal subjects to range from 0 to 14.7 microgms. In four cases of Wilson's disease, values ranging from 207 to 715 were found. In the three cases of Wilson's disease studied by us, the serum copper levels were 61.6, 136.4, and 77.4 microgms. per 100 ml. The 24 hour urinary excretions in the same patients were 197.8, 378, and 556 microgms. respectively.

In our initial study with these patients we have confirmed the results of Cummings,[2] Denny-Brown,[3] and others[8] that BAL markedly increases the

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urinary excretion of copper. However, in subsequent periods of BAL administration, it was noted in all patients that the increase in urinary excretion was not as dramatic as the initial effect. We used the treatment schedule outlined by Cummings[2] which is felt inadequate by Denny-Brown. This may explain the lack of later responses.

All of the patients showed some clinical improvement following BAL therapy. This was indicated by an increase in the amount of daily living tasks the patient could perform, the greying of the Kayser-Fleischer rings, and changes noted in the neurologic examination.

Accurate interpretation in the results of serum and urinary levels was difficult in our first experiment lacking fecal copper values. Since even in periods of lowest copper excretion these patients excreted significantly more than normal individuals, it was suggested that copper was readily absorbed and probably in excess amounts in patients with Wilson's disease. It has been found that copper is stored presumably in the liver and the nervous tissues in excessive amounts. The present paper is concerned with complete balance studies in both normal subjects and in three patients with Wilson's disease.

METHOD

Each patient was given a thorough history and physical examination and then placed on a complete balance study. Analysis of the diet for copper was carried out. The copper intake was measured by taking an aliquot of the food and liquid consumed for each three-day period. Urinalyses were performed on three-day pools, serum copper was done weekly, and fecal copper was analyzed with three-day specimens. Each patient was placed on a six-day control period at which time an additional intake of oral copper was given in the form of copper sulfate containing 3,000 mg. of copper per 24 hours. For the remaining six-day period, the patients were given a course of BAL following the schedule of Cummings.[2] Copper was estimated in the urine, feces, and food by a modified method of A. Eden and H. H. Greene.[10] Determination of the copper in the serum was based on the diethyldithiocarbamate reaction described by Gubler et al.[11] Special care was taken to see that all receptacles for the urine and all syringes for the collection of blood were copper-free as well as all apparatus used. Control blanks were put up each time. Each patient, in addition to routine laboratory tests, had studies of fasting blood sugar, serum bilirubin, bromosulfonphthalein, non-protein nitrogen, serum sodium and potassium, alkaline phosphatase, and blood calcium.

DISCUSSION

Copper is important in the body metabolism. There is some relation to erythropoiesis and, in animals, copper has some effect on myelinization in the central nervous system. Van Ravesteyn[12] reviewed the history of copper as a medication. Copper is ingested in the form of food or medication and is absorbed in the intestinal wall. From there it is retained or excreted through the feces. Other routes of excretion are through the urine, bile, and through active secretion through the intestinal mucosa. In the intestinal tract, it is

TABLE 1.

COPPER BALANCE STUDIES IN HEPATOLENTICULAR DEGENERATION AND CONTROL SUBJECTS

3-Day Periods	*Cu Intake* (γ)	*Cu Output* *Urine*	*Stool*	*Total*	*% in Stool*	*Balance*	*Serum*	*B.A.L.*
I. P.	4376.0	1046.4	1488.0	2534.4	33	+1841.6	89.03	
♀	4200.5	693.0	1656.0	2349.0	39	+1851.5	81.98	
	3905.6	2805.0	1714.0	4519.0	44	− 613.4	103.15	+
	3133.8	1968.0	1080.0	3048.0	34	+ 85.8	81.9	+
V. I.	4113.0	1549.8	1300.0	2850.0	31	+1263.0	89.03	
♀	3814.2	1414.0	1144.0	2548.0	30	+1266.2	94.0	
	3704.8	3360.0	1612.0	4972.0	43	−1267.2	57.7	+
	3082.2	1619.4	2408.0	4027.0	78	− 944.8	103.1	+
W. P.	5000	1750	2550	4300	51	700	143	
♂	5759	2238	2919	5157.0	50.5	602		
R. M.	5076.8	69.02	5244.0	5315.0	100.4	− 236.2	155.0	
♂	5148.8	45.6	4160.0	4206.0	81.5	+ 942.8		
M. D.	5700.0	60.0	5500.0	5560.0	96.5	+ 140	147.3	
♂	5757.0	67.0	5611.0	5678.0	96.8	+ 79		
O. F.	4025	40.0	3906.0	3946.0	97.5	+ 79	217.0	
♂								

Results of copper balance studies on three patients with Wilson's disease: I.P., V.L., and W.P. Results in four controls are shown also. There is a marked difference in the percentage of copper appearing in the stool between the two groups.

possible that the copper travels some sort of circuit from absorption to excretion. The experiments of Van Ravesteyn on normal patients showed that the excretion of copper in the bile was less irregular than with the feces but would rise in the bile after intravenous administration of copper. When copper was given by mouth, about 25 per cent was absorbed through the intestinal wall, and the absorbed copper was gradually eliminated. When copper was injected intravenously, there was an immediate rise in blood copper levels and a prompt fall in a few hours. A temporary rise in biliary copper appeared in a few days followed by an increase in the fecal copper. The excretion of copper through the intestinal and biliary tracts was not parallel.

The copper in the serum is almost completely in the form of a complex protein, caeruloplasmin, with a molecular weight of over 150,000. Fetal storage of copper in the liver is high, and there is a gradual decrease to the normal adult level between the fifth and fifteenth years. There are normally about 150 mg. of copper in the body, and an intake of 2 mg. per day in the adult more than satisfies the normal daily requirement. In the circulation the copper is almost equally distributed in the cells and plasma. There are many altered states in which copper is increased in the plasma, cells or storage organs, such as pregnancy, tuberculosis, carcinoma, and cirrhosis. In the plasma, copper is increased in many infections which Cartwright[13] felt may indicate that copper has some relation to defense mechanisms, although the copper increase may only be an evidence of increased metabolic activity of the cells.

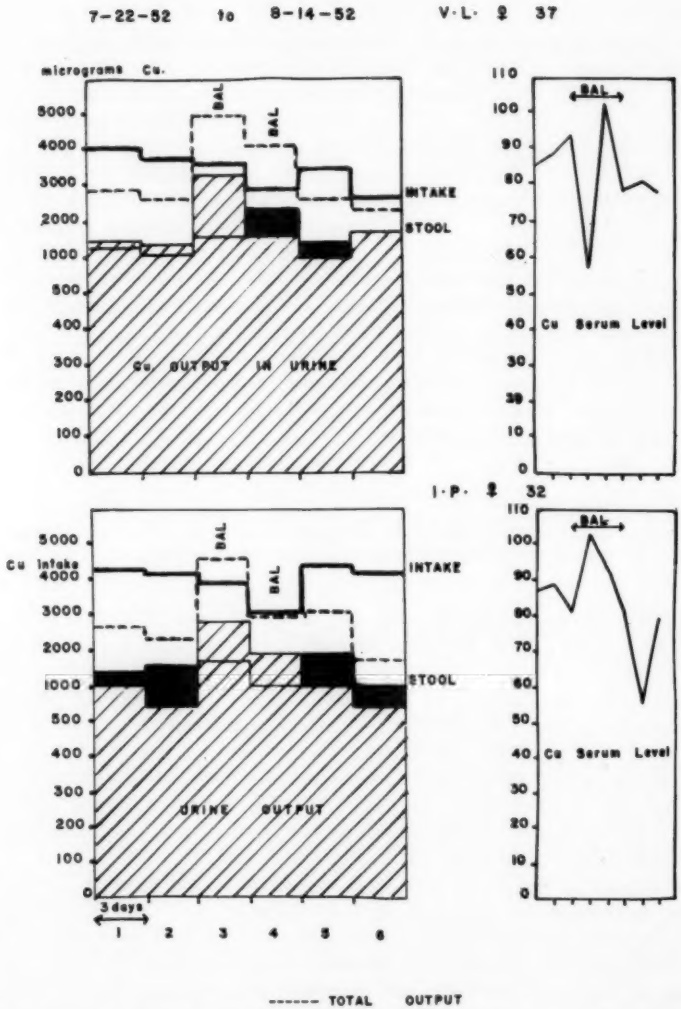

FIG. 1. Results in two patients with Wilson's disease. Urine output of copper is high. Broken line shows total output. During BAL, urine excretion increases and negative balance of copper is obtained.

RESULTS

In our studies with patients with hepatolenticular degeneration, we have found that these patients excrete much smaller amounts of copper via the

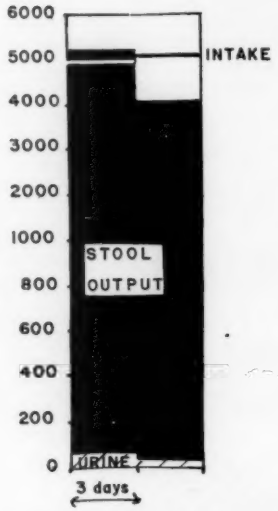

FIG. 2. Copper balance in a normal patient. There is a large output in the stool, while urine copper excretion is small compared to Wilson's disease.

stools than to the normals. There was also a marked difference in the urinary excretion as compared to the normal subjects. The patients with Wilson's disease were usually in a marked positive copper balance. There is evidence that these people absorb much more copper through the intestinal wall than the normal subjects and excrete it mostly through the urine. Patients with hepatolenticular degeneration absorb copper from their food two to three times more intensively than the normal subjects. With the administration of BAL patients with Wilson's disease increased their urinary excretion markedly and showed a negative balance of copper. The administration of BAL not only increased the excretion of copper from the daily intake, but also from copper which has been stored in the tissues of the body (table 1).

Figure 1 shows the results in two patients with Wilson's disease. In the first two periods, there is a marked excretion of copper in the urine, and the patients are in positive balance. During the administration of BAL, there is a further increase in urinary copper excretion. At this time the patients are in a negative balance, although patient I.P. still shows a slight positive balance during the second period of BAL. The percentage of copper that appears in the stool as compared to the intake varies from 30 to 78 per cent with a mean of 41.5 per cent. In figure 2 a normal subject shows a marked contrast with over 90 per cent of the copper intake being received in the stool.

In figure 3, W.P., a patient with Wilson's disease, and M.D., a normal control, are shown. The marked difference between stool and urine output is evident. With an increased intake of copper orally, W.P. retained 48 per cent of the ingested copper, while M.D. retained only 5.2 per cent. In the normal subject BAL increases the urine output slightly. There is an increase in the copper output of the stool and the patient is in a negative balance. The increase in the stool which contains more copper than the intake may be due to fecal retention or to some stimulation of either bile or intestinal excretion. This must be investigated further.

In figure 4, studies on a control, M.D., and I.P. with Wilson's disease, are shown. Again the marked difference in stool and urine output can be seen. Even on BAL, patient I.P. retained more than was excreted during the period of increased oral copper. When a normal diet was resumed, she again excreted more than the intake.

TABLE 2.

EFFECT OF RESIN ON COPPER IN HEPATOLENTICULAR DEGENERATION AND CONTROL SUBJECT

Cu Intake (γ)	*Cu Output*			*Balance*		*Cu Intake*	*Cu Output*			*Balance*
M.D. ♂	*Urine*	*Stool*	*Total*		*W.P.* ♂		*Urine*	*Stool*	*Total*	
House Diet						*House Diet*				
5700.0	60.0	5500.0	5560.0	+ 140.0		5000.0	1750.0	2550.0	4300.0	+ 700.0
5757.0	67.0	5611.0	5678.0	+ 79.0		5759	2338.0	2919.0	5157.0	+ 602.0
6868.0	187.0	6577.0	6764.0	+ 104.0						
3000 γ Cu p.o./24 hrs.					3000 γ Cu 24 hrs.					
17984.0	250.0	10528.0	10778.0	+ 7206.0		14350	2500.0	4100.0	6600.0	+7750.0
28206.0	185.0	10825.0	11010.0	+ 5732.0		15275	3225	4530.0	7755.0	+7520.0
Resin 45 qms. q. d. 3000 γ Cu p.o./24 hrs.					Resin 45 qms. 3000γ Cu/24 hrs.					
13297.0	105.0	26598.0	26703.0	−13406.0		15603.0	2792	7328	10120	+5483.0
14341.0	45.0	15624.0	15669.0	− 1328.0		15200.0	2550.0	7320	9870	+5330
Diet and Resin only					Diet and Resin					
5633.0	104.0	11160.0	11264.0	− 5631.0		7428	2402	6949	9351	−1923
7048.0	205.0	12790.0	12995.0	− 5947.0		7500	2463	7001	9464	−1964

Results of the effect of a sodium polystyrene sulfonate resin are shown in a normal subject, M.D., and patient W.P. with Wilson's disease. Both patients were in a negative balance while on a normal house diet and resin alone.

Two patients, M.D. and W.P., were given a sodium polystyrene sulfonate resin.* Because exchange resins have been used to remove the sodium in patients with heart failure, we were interested to see if this resin would remove copper and possibly give us another method of treatment in patients with Wilson's disease. After a control period, the patients were placed on 15 gm. of resin three times daily. It was found that this resin did bind the copper and remove it through the stool. Figure 3 shows the effect on patient W.P. There was a definite increase in the stool copper. On a normal diet a negative balance of copper was obtained. Figure 4 shows the effect of the resin on patient M.D. There was a marked increase in fecal copper and, on resumption of a normal diet, this continued in even greater proportion. Table 2 shows these copper values in both patients. W.P. continued to absorb copper

*Kindly supplied by Dr. Evan W. McChesney of Sterling-Winthrop Research Institute, Rensselaer, New York.

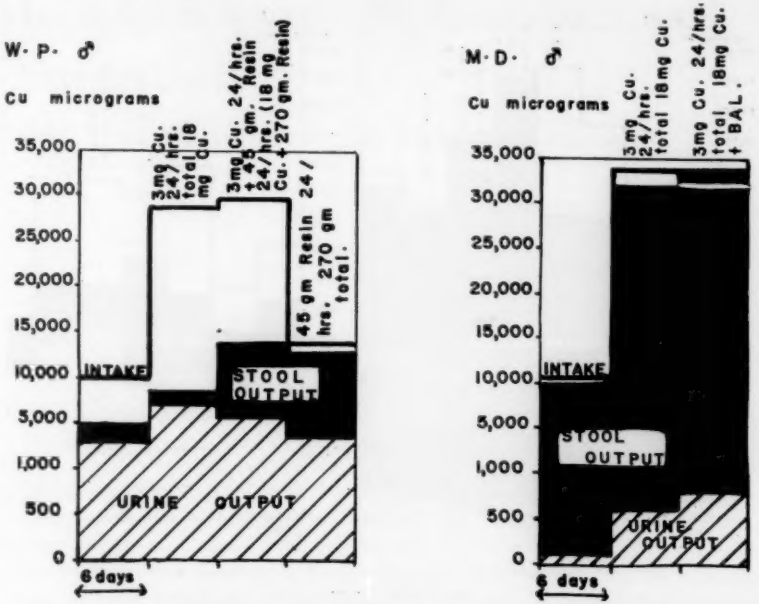

FIG. 3. The marked difference between urine and fecal copper excretion is illustrated in two patients, W.P. with Wilson's disease, and M.D., a normal control. With an oral increase of 3000 micrograms. of copper daily, W.P. absorbed 48 per cent, while M.D. absorbed only 5.2 per cent. On resin, W.P. increased fecal copper output while urine copper decreased slightly. This was continued on a normal diet. M.D. increased urine output from body storage depots on BAL.

even with resin on an increased oral intake. Further studies on this patient, while on a normal diet and resin, have shown definite clinical improvement.

SUMMARY

Studies on copper metabolism of both control subjects and patients with Wilson's disease have shown that there is an increased intestinal absorption of copper in the latter patients. This defect probably accounts for the increased storage of copper found in hepatolenticular degeneration. There is always a marked increase in the 24 hour urinary excretion of copper found in Wilson's disease as compared to normals. BAL increases this urinary excretion and probably improves the patient. An exchange resin removes copper via the stool. This is more pronounced in normals but may prove to be beneficial in the treatment of patients with Wilson's disease.

The technical assistance of Miss Vera Rosenberg, Mr. Roy Rand, and Mr. Robert Martin is gratefully acknowledged.

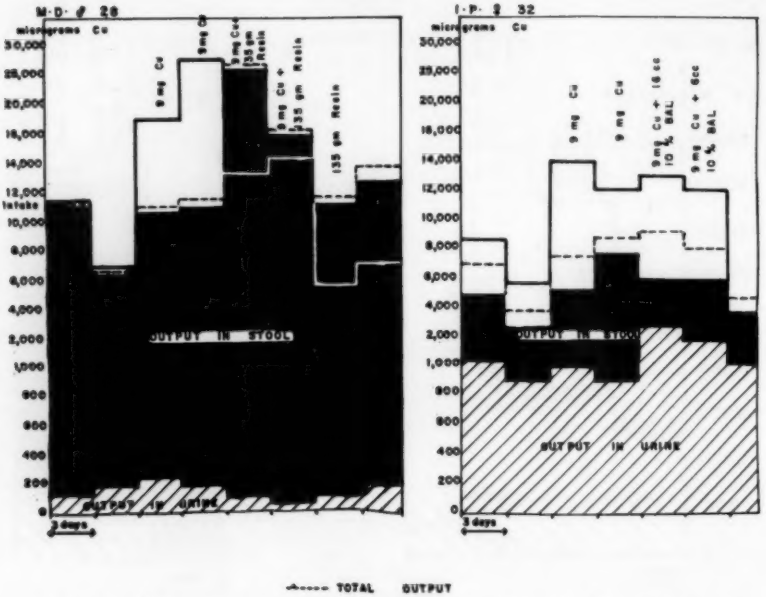

FIG. 4. A further balance study on a normal control, M.D., and I.P., with Wilson's disease. On resin, M.D. showed a marked increase in fecal copper excretion and thereby produced a negative balance. The effect of BAL on I.P. is shown. The broken line represents total output of copper. The solid line represents total intake.

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Multiple Sclerosis: Its Frequency and Distribution

With Special Reference to Denver, Colorado

Leonard T. Kurland, M.D., Dr. P. H.
and H. J. Dodge, M.D., M.P.H.

DURING the early months of 1949, a study of the frequency of multiple sclerosis in Denver, Colorado, was begun. This was one of a series of epidemiologic investigations sponsored by the National Multiple Sclerosis Society "to determine the extent of multiple sclerosis in the United States and Canada and to study the influence of climate and race on the distribution of the disease." Similar studies were also conducted through local university medical facilities in the metropolitan districts of New Orleans and Winnipeg and the cities of Boston and San Francisco. These areas were selected because they are major cities with comparable standards of medical practice but have differences in climate, geographic latitude and racial composition of the population as shown in table 1.

THE present paper is concerned with the findings in Denver as compared with those of the other study areas for which data are available. At the time of writing only the San Francisco data have not been analyzed.

The detailed description of the method of study has been reported elsewhere[1] and will merely be summarized here: Under the direction of the staff members of the local universities, medical students were employed and trained in abstracting hospital and clinic records and in contacting physicians to review their records. Reports of the diagnosed and suspected multiple sclerosis cases and deaths were obtained from all registered hospitals, including outpatient departments, clinics and nursing homes, and the local office of vital statistics in all cities for the ten year period 1939 to 1948, inclusive. In addition, physicians in private practice were requested, by letter and telephone, to provide reports on cases seen in the previous five years and to identify any patients who were still known to be alive regardless of when they were last seen. No case was interviewed in person.

From the National Institutes of Health, U.S.P.H.S., and the department of preventive medicine and public health, University of Colorado School of Medicine, Denver.
This study was supported by a grant from the National Multiple Sclerosis Society.

TABLE 1

COMPARISON OF THE STUDY AREAS AS TO DIFFERENCES IN POPULATION CHARACTERISTICS, LATITUDE, AND CLIMATE

	Denver	*Boston*	*Winnipeg*	*New Orleans*
Total population*	415,800	846,100	313,600	601,600
Nonwhite population	4%	3% (est.)	Negligible	28%
Increase in population last 10 years	29%	6%	11%	10%
Latitude	40°N	42°N	50°N	30°N
Altitude	5,280 ft.	21 ft.	760 ft.	5 ft.
Mean temperature				
January	31°F.	28°F.	−3°F.	55°F.
July	73°F.	72°F.	66°F.	83°F.
Annual rainfall-inches	14 in.	41 in.	20 in.	57 in.

*Winnipeg population, census June 1, 1946; New Orleans population, estimate, April 1947; Boston and Denver populations, census April 1, 1950.

In 1952 all important sources of cases in the 1949 study were reexamined for additional cases diagnosed in the interim. However, only those cases whose onset of symptoms had occurred before January 1, 1949 have been included here. At the same time, duplicate records on each patient were consolidated and the patient's living or dead status and latest diagnosis were established to as recent a date as possible. Each case was classified as "probable" or "possible" according to the opinion of the physician making the most recent diagnosis. Probable cases were those in which clinical evidence was consistent with the diagnosis where other possibilities were reasonably excluded, while possible cases were those in which no single diagnosis had been established.

In this series of studies, January 1, 1949 was taken as the prevalence day as a point of reference in time. Cases of multiple sclerosis residing in the given study area on this date were used in determining the prevalence of the disease. The number of persons known to have developed or died from multiple sclerosis during the years 1939 to 1948, inclusive, were used for calculation of incidence and mortality rates.

The term prevalence, as used here, refers to the amount of disease found in a community as of a particular date, without regard to the time of onset of any case. The term incidence, on the other hand, refers to the amount of disease newly developed in a given time period, usually a year. Thus the two terms are quite distinct in their implications. In general, prevalence reflects the aggregation of cases over a period of years, while incidence reflects the development of new cases in a specified time period.

RESULTS

A total of 256 cases were reported in the Denver study. Of these, 189 were classified as probable, 47 were classified as possible, and for 20, only death certificates were found. In view of the fact that the reliability of diagnosis and the time of onset were uncertain for the latter 20, they are not included in statistical analyses for incidence and prevalence, although they will be dis-

TABLE 2

CLASSIFICATION OF MULTIPLE SCLEROSIS CASES BY CERTAINTY OF DIAGNOSIS
1949 SURVEY

Case Reports classified as	Denver		Boston		Winnipeg		New Orleans	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Probable	189	80	509	74	172	79	94	72
Possible	47	20	179	26	47	21	36	28
Total	236	100	688	100	219	100	130	100

cussed in the section on mortality.

The number of cases in the probable and possible categories for Denver and the other cities is presented in table 2. About three fourths of the cases in each city were classified as probable. Because the diagnosis in the possible cases is of a low degree of reliability, only the probable cases are used in determining the frequency rates and ratios.

Table 3 shows the breakdown of probable cases as to living or dead status on January 1, 1949. It is seen that in the Denver study, approximately two thirds of the cases are female. There is no striking difference in the distribution by living or dead status for the two sexes.

Comparison of the four study areas as to living or dead status as of January 1, 1949 shows no great difference.[1] Those cases living in the specified city on the prevalence date, in relation to the total cases for each city, ranged from a high of 86 per cent in Denver to a low of 69 per cent in Boston. Winnipeg and New Orleans were in the intermediate positions with 76 per cent and 74 per cent, respectively.

To ascertain the amount of disease present in a population at a given time, prevalence ratios are determined. In order to be more specific, the cases

TABLE 3

DISTRIBUTION OF DENVER CASES OF MULTIPLE SCLEROSIS
By Living or Dead Status on January 1, 1949, by Place of Residence and by Sex, All Races

Status	SEX					
	Male		Female		Both Sexes	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Living	53	82.8	109	87.2	162	85.7
In Denver	52	81.2	102	81.6	154	81.5
Elsewhere	1	1.6	7	5.6	8	4.2
Died Between 1/1/39 & 1/1/49	8	12.5	11	8.8	19	10.1
In Denver	6	9.4	9	7.2	15	7.9
Autopsy confirmed	0	0.0	2	1.6	2	1.1
Elsewhere	2	3.1	0	0.0	2	1.1
Status unknown	3	4.7	5	4.0	8	4.2
Total cases	64	100.0	125	100.0	189	100.0
Percent of total	34.8		65.2		100.0	

TABLE 4

AGE, SEX, AND RACE SPECIFIC PREVALENCE RATIOS (PER 100,000 POPULATION) FOR MULTIPLE SCLEROSIS CASES LIVING IN DENVER ON JANUARY 1, 1949

Age on Jan. 1, 1949 (years)	Male		Female		Both sexes	
	Number of cases	Prevalence ratios per 100,000	Number of cases	Prevalence ratios per 100,000	Number of cases	Prevalence ratios per 100,000
White						
0 to 14	0	0.0	0	0.0	0	0.0
15 to 24	3	11.2	5	17.1	8	14.3
25 to 34	16	47.9	41	116.8	57	83.2
35 to 44	15	54.6	30	100.1	45	78.4
45 to 64	12	29.2	23	51.2	34	40.6
65 and over	3	18.4	3	13.9	6	15.8
Unknown	1	...	0	...	1	...
All ages	50	26.1	102	49.5	152	38.2
Non-white						
0 to 34	0	0.0	0	0.0	0	0.0
35 to 44	2	150.0	0	0.0	2	74.4
45 and over	0	0.0	0	0.0	0	0.0
All ages	2	21.7	0	0.0	2	11.0
All races						
0 to 14	0	0.0	0	0.0	0	0.0
15 to 24	3	10.6	5	16.3	8	13.5
25 to 34	16	45.4	41	110.8	57	78.9
35 to 44	17	59.1	30	95.8	47	78.2
45 to 64	12	28.0	23	49.4	35	39.2
65 and over	3	17.7	3	13.5	6	15.3
Unknown	1	...	0	...	1	...
All ages	52	25.9	102	47.4	154	37.0

of the disease under study are grouped on the basis of age, sex, race, or other relevant characteristics. The number of cases in each group is then divided by the number in the total population having the same age, sex, race, or other characteristics as the group and the result is adjusted to some base number (usually 100,000). The final result is a specific ratio per unit of population. By this manipulation, one achieves a basis for comparison between and among groups.

In this study, prevalence ratios specific for age, sex, and race were determined, using the 154 cases classified as probable multiple sclerosis known to be living in the study area on January 1, 1949, as shown in table 4 and figure 1.

It is seen that the prevalence rises sharply to a peak in the age range of 25 to 34 years for white females and less gradually to a peak at 35 to 44 years for white males. The prevalence ratio for the total nonwhite population is only 11.0 per 100,000 population. The latter figure is based on the two nonwhite cases reported (both males in the 35 to 44 age group). Little reliance can be placed on the nonwhite prevalence figure, however, for several reasons.

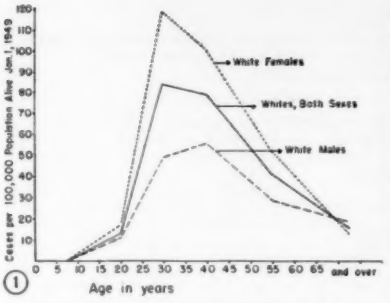
Cases per 100,000 Population Alive Jan. 1, 1949
White Females
Whites, Both Sexes
White Males
0 5 10 15 20 25 30 35 40 45 50 55 60 65 and over
Age in years
1

FIG. 1. Age-sex specific prevalence ratios for whites, Denver.

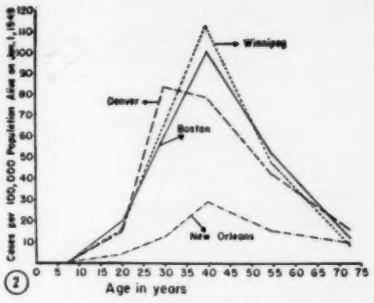
Cases per 100,000 Population Alive on Jan. 1, 1949
Winnipeg
Denver
Boston
New Orleans
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Age in years
2

FIG. 2. Age specific prevalence ratios for whites, four cities.

First, the nonwhite population is so small (18,252) that by chance alone one might reasonably expect a difference of this degree. We believe that another, and perhaps even more important factor, must also be considered. From 1940 to 1950, the nonwhite population increased 112 per cent in contrast to a 27 per cent increase in the white population. The increase in the nonwhite population was predominantly in the age group 24 years or younger, where the risk of multiple sclerosis is not as great as in subsequent age groups. Furthermore, it is probable that much of the increase in the nonwhite population consists of persons or families in which the adults migrated to Denver primarily to obtain employment. These persons would not only be younger but were probably healthier individuals than those in the populations from which they were drawn. These newer immigrants then should be a healthy group to start with and, because they are newer residents, would not have been exposed to the same period of risk for developing the disease as the white population who were permanent residents of the Denver area.

The nonwhite ratios for Denver are not shown in figure 1 because they would distort the picture. That they make relatively little difference in the total picture can be seen in table 4 by the comparison of the ratios for whites with the ratios for all races.

In Denver, the prevalence ratio for white females of all ages is almost double that for white males of all ages, the ratio of the female rate to that of the male rate being 1.9. The greater prevalence in females appears to be constant, for these ratios were 1.7, 1.6, and 1.4 for white populations in Boston, Winnipeg, and New Orleans, respectively.

In figure 2 the age specific prevalence ratios for whites, both sexes, in Denver are contrasted with similar ratios for Boston, Winnipeg, and New Orleans. It will be seen that the curve for Denver does not differ materially from that of Winnipeg and Boston, except that the peak is somewhat earlier and lower. It is likely that some of the difference in prevalence ratios in the four cities is due to variations in the method of estimating the base population

TABLE 5

INCIDENCE AND AVERAGE ANNUAL INCIDENCE RATES BY AGE AND SEX, MULTIPLE SCLEROSIS DEVELOPING IN DENVER'S WHITE POPULATION DURING 1939 TO 1948, INCLUSIVE

Age at onset (years)	Male		Female		Both sexes	
	Number of cases	Average annual cases per 100,000	Number of cases	Average annual cases per 100,000	Number of cases	Average annual cases per 100,000
0 to 14	0	0.0	1	0.2	1	0.1
15 to 24	1	0.4	15	4.8	16	3.0
25 to 34	12	3.9	32	9.6	44	6.9
35 to 44	5	1.8	7	2.3	12	2.1
45 to 64	2	0.5	8	1.7	10	1.1
65 and over	1	0.7	0	0.0	1	0.3
Unknown	4	..	2	..	6	..
All ages	25	1.3	65	3.1	90	2.3

numbers. Furthermore, with Denver's rapid gain in population between 1940 and 1950, the greatest relative gains among whites were in the age groups of 14 years or less and 65 years or more. Neither group is at great risk of developing multiple sclerosis. At any rate, analysis indicates that for white populations, Denver's overall prevalence ratio per 100,000 population (38.2) is significantly higher than that of New Orleans (12.9), but does not differ to any statistically significant degree from Winnipeg (41.8) or Boston (41.3), either singly or combined.

In order to assess the frequency with which new cases occur in Denver, incidence and incidence rates were determined. Table 5 gives the breakdown by age at onset and sex in the white population, where onset occurred in Denver during the ten year period 1939 to 1948, inclusive. Also given are the average annual age and sex specific incidence rates for the ten year period.

It will be seen from this table that the onset of multiple sclerosis begins at an earlier age in females than in males in Denver. In both sexes the peak is reached in the age group of 25 to 35 years and then declines rapidly. The ratio of female to male average annual incidence rates is 2.4, somewhat higher than the ratio of the prevalence rates. The corresponding ratios for the other cities already studied are 1.9, 1.5, and 1.9 for Boston, Winnipeg, and New Orleans, respectively.

In the period from 1939 through 1948 in Denver, an average of 8.5 cases of multiple sclerosis developed each year, 2.2 cases in males and 6.3 cases in females. These averages probably understate the true situation because of the lag between onset of the disease and its diagnosis. The possible reasons for differences of prevalence and incidence by sex are discussed in an earlier paper.[1]

Comparison of age specific average annual incidence rates for the four cities are shown in figure 3. It will be seen that the curves for Denver and

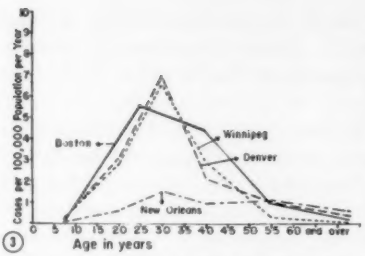

FIG. 3. Age specific average annual incidence rates for whites, four cities.

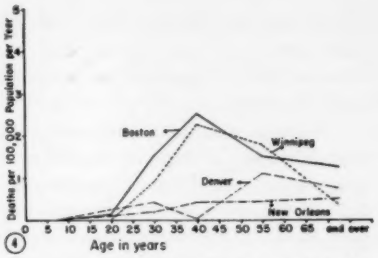

FIG. 4. Age specific average annual death rates, all races, four cities.

Winnipeg are almost identical and not greatly different from Boston. The curve for New Orleans differs appreciably from the others.

For the Denver study, estimates of mean age at onset of multiple sclerosis and mean years of duration of the disease were calculated but are not reported because we believe that they are not sufficiently reliable. Methods of study other than the retrospective one used here are necessary if acceptable estimates of average onset age and years of duration are to be achieved.[2,3]

Mortality rates in the Denver study are given as a matter of record. It should be realized that there were only 17 deaths attributable to multiple sclerosis by the criteria of the present study; such a small number that little reliance can be put in the age specific rates. However, for comparison, the Denver experience is plotted against that of the three other cities in figure 4. For Denver the average annual white death rate per 100,000 of population, during the ten year period prior to January 1, 1949, was 0.53 for females and 0.31 for males, a ratio of 1.7 to 1. Denver's overall white death rate for multiple sclerosis of both sexes and all ages was 0.42 per 100,000 per year in comparison with 1.17, 0.93, and 0.23 for Boston, Winnipeg, and New Orleans, respectively.

With regard to mortality, Denver would seem to fall somewhat between the pattern of New Orleans on the one hand and Winnipeg and Boston on the other. However, in addition to the 17 probable cases in which death occurred there were 20 additional cases in Denver from 1939 to 1948 reported by death certificates only. In the other cities, only 25 per cent of the deaths were reported by death certificates only. In these cities, the considerable effort and time expended to trace case reports for such death certificates were more successful than in Denver. In Denver, most of the physicians who had signed such death certificates in the previous ten years (i. e., without providing a corresponding case report for the survey) could not be reached during the survey and some of those who were reached were unable to supply any lead as to the source of a detailed case report.

In this respect, it is of interest that from January 1949 to January 1952, there were 13 multiple sclerosis deaths (eight males and five females) for

which case reports had been collected in the original survey. For this three year period, the average annual multiple sclerosis mortality rate was thus 1.04 per 100,000 population, a rate comparable to that found in both Boston and Winnipeg.

There is another factor unique to Denver among the cities studied that may account for some of the difference in mortality. This is the greater rate of growth of the Denver population in the last decade. Whereas the population of the other cities increased at the rate of about 6 to 11 per cent, the population of Denver increased 29 per cent. The average duration of multiple sclerosis is probably about 20 years; consequently, the number dying from 1939 to 1948 would theoretically be dependent on the incidence of the disease in the population of an earlier decade. (This assumes that newer immigrants to Denver have less active and advanced multiple sclerosis than the resident population. This item was considered in relation to the nonwhite Denver prevalence ratio.) However, mortality rates were determined by dividing the number of recent deaths by the present (1950) population and this has the effect – in Denver to a greater extent than in the other cities – of lowering the mortality rates for the period from 1939 to 1948.

In the three year period from January 1949 to January 1952, the period which we believe presents a more accurate picture of the multiple sclerosis mortality in Denver, the case fatality rate was approximately 3 per cent per year. This is based on the 13 deaths in this period among the 154 probable cases living in Denver on January 1, 1949.

From 1939 to 1948, the diagnoses were confirmed by autopsy in only two reported cases. In the three year period from 1949 to 1952, of the 13 deaths reported, the diagnoses in six were confirmed by autopsy.

DISCUSSION AND SUMMARY

Epidemiologic characteristics of multiple sclerosis in Denver, Colorado, were studied for the ten year period prior to January 1, 1949. This report compares the results in Denver with those of Boston, Winnipeg, and New Orleans, where similar investigations were conducted.

The prevalence ratio of multiple sclerosis in the white population of Denver was found to be 38.2 per 100,000 per year. This is similar to the ratios per 100,000 population reported for Winnipeg (41.8) and Boston (41.3) and is about three times that reported for New Orleans (12.9). Only two cases were reported in the small nonwhite population of Denver, and no conclusions regarding differences between the white and nonwhite prevalence can be drawn.

The average annual incidence rate in Denver was 2.3 per 100,000 population per year. This too is similar to the rates per 100,000 population in Boston (2.6) and Winnipeg (2.2) and is about three times higher than that found in New Orleas (0.8).

The female to male ratio in both prevalence and incidence is about 2:1

for Denver. Incidence and prevalence (but not mortality) were also higher for females in the other cities.

The average annual mortality rate in Denver (0.42 per 100,000 population per year) is between that for New Orleans on the one hand (0.23) and for Boston (1.17) and Winnipeg (0.93) on the other hand. Reasons are stated why the authors believe the mortality in Denver should be similar to that in Winnipeg and New Orleans. In support of this, the average annual mortality in Denver for the period January 1949 to January 1952 was found to be 1.04 per 100,000 population per year. It would appear that for the white population, the prevalence, incidence and mortality of multiple sclerosis in Denver is similar to that in Boston and Winnipeg and is about three times higher than that in New Orleans.

Denver, Boston, and Winnipeg have in common a north latitude of 40° or more and cool to cold climates, in contradistinction to New Orleans with a north latitude of 30° and a warm to hot climate. It thus seems probable, as others have suggested before, that some factors related to climate influences the frequency of multiple sclerosis. Unfortunately, there is insufficient information to indicate that the prognosis of multiple sclerosis in the southern community is any better than that of patients in the northern communities.[3]

It is hoped that this report may be helpful in suggesting some reasonable course of investigation of etiology. A corollary to this could be that any hypothesis that may be developed to explain causes should account for the variations in geographic distribution which have been described.

The authors are indebted to the physicians of Denver for their gratifying response; to the physicians, clinics, and hospitals who made their records available for confidential study; to the Colorado State Department of Public Health for access to death certificates; and to the group of medical students who collected the basic morbidity data.

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Primary Brain Tumors in Patients Over Age 60

Charles Rupp, M.D., Helena E. Riggs, M.D., H. W. Hogan, M.D. and James A. L. Moulton, M.D.

PRIMARY BRAIN TUMORS in individuals age 60 and older are not uncommon. Monroe[1] reported an incidence of 0.2 per cent of primary cerebral neoplasms in a large unselected group of persons older than 61. Although the clinical and pathologic features have been well delineated by Moersch, Craig and Kenohan,[2] Hastings[3] and others, brain tumors in the elderly are frequently overlooked by the clinician and the true diagnosis is revealed only at autopsy. Therefore it seemed of interest to review 100 cases in which such tumors were discovered at necropsy or operation.

INCIDENCE

These 100 cases include all brain tumors found either at operation or necropsy in patients over 60 admitted to the Philadelphia General Hospital between the years 1920 and 1951 inclusive. The age distribution of the group was as follows:

60 to 69 years	66
70 to 79 years	26
80 to 89 years	5

The cases were approximately equally distributed between the two sexes.

In 25 cases, the neoplasm was only an incidental necropsy finding in patients who died of unrelated somatic disease. Twenty-one of these presented meningiomas of the vertex or convexity measuring less than 2.5 cm. in diameter. Chromophobe adenomas entirely confined to the anterior lobe of the pituitary were present in two. A colloid cyst of the third ventricle and an ependymal hamartoma of the fourth ventricle, neither of which had caused any degree of ventricular obstruction, completes this group in which clinical neurologic findings were either insignificant or absent.

In the 75 patients who presented symptoms suggestive of focal neurologic disease during life, delay in seeking hospitalization was outstanding. Sixteen were stuporous on admission and 24 died within a week. Disturbed mental status or aphasia made satisfactory examination difficult in 39. In 16 cases

From the neurologic wards and laboratories of the Philadelphia General Hospital, Philadelphia, Pennsylvania.

Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 10, 1953.

far advanced mental deterioration, contractures, decubiti or incontinence subsequent to severe neurologic involvement precluded adequate study. Therapy was of necessity limited to terminal care. In 15 patients acute myocardial infarction, advanced congestive failure, uremia or severe acute infections overshadowed the neurologic disorder.

Forty-four patients were admitted primarily for the diagnosis and treatment of their neurologic disorder. These patients were somewhat younger. Only 12 per cent were over 69 years of age as compared to 40 per cent of the two preceding groups. Even in these patients, hospitalization was often sought only when progression of the disease became greatly accelerated or an acute exacerbation of symptoms occurred. Thirteen died within a week of admission. Neurologic manifestations had been present for less than three months in 17, longer than one year in eight, and for seven, 15, and 20 years respectively in three patients.

Although there was no uniformity in the location or type of neoplasm in these 44 patients, certain findings were common to the group as a whole.

Increased Intracranial Pressure

It has been stated that signs of increased intracranial pressure are not conspicuous in the elderly.[3] Headache, vomiting, lethargy and mental obtundity, however, preceded any other symptoms for from two weeks to six months in 11 and developed during the clinical course in ten others. In six additional cases, intracranial hypertension was demonstrated by funduscopic examination, spinal fluid study, or roentgenographic examination of the skull.

Psychic Disturbances

Alterations in the psychic sphere in the nature of mental deterioration, personality change, loss of memory, poor judgment, confusion, disorientation or agitation were present in 27. In nine these were the presenting symptoms frequently preceding the development of other neurologic findings by longer than three months. Six developed mental disturbances late in the course. In contrast to the group of patients with long-standing senile deterioration, there was a progressive development of associated neurologic manifestations.

Seizures

Generalized convulsions beginning in middle life were the first manifestations of neurologic dysfunction in ten; in five cases they persisted without further development of neurologic defect for a period of one to ten years. In the remaining cases, seizures preceded the onset of other signs and symptoms by only ten days to two months.

Motor Paralysis

Hemiplegia or hemiparesis developed in 36 of the 44 patients in this group. Motor deficit initiated the illness in 14, and appeared only late in 18. Apoplectic onset simulating a cerebral vascular accident occurred in eight, and was associated with Jacksonian convulsions in four. Slow progressive paralysis over a period of several days to two weeks was noted in nine. In one patient

complete hemiplegia developed slowly over a period of one year. Two patients with right-sided hemiplegia became aphasic one and two years after the development of paralysis. In contradistinction to the course of hemiplegia associated with cerebrovascular disease, 30 of the patients showed an essentially progressive course. Symptoms of increased intracranial pressure preceded paralysis in 11. Antecedent or concomitant psychic disturbances were present in 11. Nine had focal or generalized convulsions, either preceding or following the paralysis.

LABORATORY FINDINGS

Because of failure to suspect the correct diagnosis and/or on account of the advanced stage of the disorder, laboratory studies were frequently incomplete. Yet, when performed, they often were helpful.

Spinal fluid: The spinal fluid pressure was elevated in 11 of 18 cases in which pressure estimations were performed. Protein was definitely elevated in 13 cases ranging from 80 to 600 mg./100 cc. and, in ten of these, was more than 150 mg./100 cc. The colloidal gold curve showed diverse alterations in five of the eight cases in which the study was made.

Ophthalmologic studies: Funduscopic studies were performed in only 22 cases. Papilledema was present in 16, while in six the fundus was either normal or showed only arteriosclerotic changes. In only one patient in whom both fundus and spinal fluid pressure studies were made were these examinations within normal range.

Roentgenographic studies: X-ray study of the skull was made in 12 patients. A pineal shift was demonstrated in four, and erosion of the dorsum sella and clinoids in one. In seven cases, roentgenographic studies were negative.

PATHOLOGIC FINDINGS

Of the 75 patients in whom space-taking lesions were present, gliomata were found in 53, meningioma in 17, chromophobe adenomas of the pituitary in four and an epidermoid tumor and a perineural fibroblastoma of the auditory nerve in one case each, respectively.

The type of gliomata found were as follows:

Spongioblastoma multiforme	19
Spongioblastoma ependymale	2
Spongioneuroblastoma	2
Astrocytoma – Grade I	9
Astrocytoma – Grades II–IV	12
Neuroblastoma	2
Ependymoma	1
Type not specified	6

Thirty-six of the gliomata involved the frontal or temporal lobes, seven originated in the corpus callosum, eight in the parietal-occipital area and two within the subcortical nuclei. The meningiomas involved the convexity or

vertex in ten, the sphenoid ridge in four, the olfactory groove in two, and the region of the foramen magnum in one.

DISCUSSION

Because of increased longevity with a greater percentage of the total population surviving into the later decades of life, evaluation of the neurologic disorders occurring in elderly patients is of increasing importance. In the years 1935 to 1941 inclusive, brain tumors in patients 60 years of age or older occurred only once in every 362 brain necropsies performed at the Philadelphia General Hospital, whereas in the years 1942 to 1952 inclusive the frequency increased to one out of every 150 necropsies.

A number of factors contribute to the failure to diagnose a brain tumor clinically in elderly patients. Chief among these is the prevalence of concomitant cardiovascular disease. Neurologic symptoms are often erroneously attributed to vascular causes without due consideration of other possible etiologic factors. A certain degree of neurologic and psychiatric deterioration is often accepted as a normal expectation in the elderly by families and local physicians. This frequently leads to a long delay before hospitalization. On admission, the neurologic condition may be so far advanced or so complicated by serious extraneural disease that adequate study is impossible. The frequent occurrence of psychiatric symptoms and aphasia further complicates satisfactory examination. Laboratory and other ancillary studies are often omitted because of the disturbed mental state and the advanced age of the patients. This is particularly true of funduscopic and spinal fluid examinations.

While an unawareness of the frequency of brain tumors in the elderly may account for a low index of suspicion, our studies indicate that the clinical manifestations are no different than in younger patients.

Certain features in the development of symptoms may assist in differentiating these cases from cerebral vascular accidents. While a large proportion of the tumor patients developed hemiplegia, this was frequently progressive whereas in vascular disorders the degree of paralysis is much more likely to attain a maximum early in the course. In vascular lesions prodromal symptoms are usually of shorter duration and convulsions are much less frequent as early manifestations.

While consideration of the above factors may lead to more accurate clinical diagnosis, the value of therapy in brain tumors in the elderly still requires individual consideration. Forty-three per cent of the 86 operated cases in Moersch's[2] series succumbed shortly after surgery. The presence of serious complicating somatic disease renders the results of surgical intervention doubtful even if the brain tumor itself is not malignant. Attention is called to the fact that gliomata comprised more than two-thirds of the brain tumors found in this series and that the greater number of these were of a malignant type. Furthermore, extensive hemorrhage into the tumor was noted in 26 cases. Eight of our patients were considered as reasonably good operative risks. Seven of these had gliomata. One died the day of operation, and the other

six survived for from ten days to four months postoperatively. The average survival period was one month. One case with a meningioma is still alive three years after operation.

SUMMARY

Brain tumors occurring in patients over 60 years of age, while not uncommon, are frequently unrecognized during life. The clinical manifestations do not differ from those found in younger age groups but are often overshadowed by concomitant somatic disease. As a result, clinical studies are often inadequate. A higher index of suspicion and more complete investigation should establish the correct diagnosis, but the high prevalence of gliomas as well as the poor general physical status of the patients limits successful surgical intervention.

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The mutual relation of the motor and special sense-centres in the cortex of the brain, ascertained by Hitzig and Ferrier, enables us to understand something of the progress of seizures. They do this, whether we regard epilepsy as a cortical disease or not, because Burdon- Sanderson's researches show that the relation is similar in the lower centres. For instance, a fit beginning in the face or tongue, if it involves the limbs, takes the arm before the leg, and we find that the arm-centres intervene between those for the face and tongue, near the fissure of Sylvius, and those for the leg, in the upper part of the hemisphere. Again, in a fit beginning with twitching of the angle of the mouth, rotation of the head commonly succeeds, and the centre for rotation of the head is situated in front of, and contiguous to, the centre for the action of the zygomatic muscle. But in other cases it is difficult to understand the progress of the aura from the experimental facts. For this there are probably three reasons: – First, we know little of the degree of structural association or separation of these centres, the cerebral sulci, of course, affording no information on the matter; secondly, the centres represent in many cases complex movements, and fits begin usually with simple movements; thirdly, we are almost ignorant of the mutual relations of the sensory centres for the limbs, which Ferrier's experiments locate on the inner aspect of the temporo-sphenoidal lobe. The facts of many aurae make it probable that these, rather than the motor centres, lead in the discharge, and determine the course of the commencing fit.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Action Potentials in Muscular Atrophy of Neurogenic Origin

*Fritz Buchthal, M.D. and Paolo Pinelli, M.D.**

IT IS well established that electromyography can be of considerable aid in the diagnosis and prognosis of muscular atrophies caused by affection of the lower motor neuron.[1] In these cases, in contrast to normal muscle and myopathies, individual action potentials can be discriminated during maximal effort without interference from the discharge of neighboring motor units; an increase in the duration of the individual action potentials has been found;[2] and spontaneous discharges of short duration occur in the apparently relaxed muscle.[3] These fibrillation potentials are considered specific for partial or total denervation.

It is the aim of the present paper to evaluate the diagnostic significance of the increase in action potential duration more closely. A systematic study has been performed with respect to the frequency of its occurrence, its possible correlation with other properties of the electrical response and with the site of the lesion in the motor neuron.

METHOD

Action potentials analysis was performed in 66 cases with muscular atrophy of neurogenic origin. In 34 of these, the lesion was localized to the peripheral nerve and consisted of a partial transection in 15, a contusion in three, and compression, perineuritis, and neuritis in 16. In 18 patients there were signs of involvement of the anterior horn cells of the spinal cord:** 13 cases of amyotrophic lateral sclerosis, three of infantile progressive spinal atrophy (Werdnig-Hoffmann), and two of syringomyelia. In the remaining 14 cases, either both central and peripheral nerve pathways were involved or the site of the lesion in the lower motor neuron was uncertain.

As many different action potentials as possible were recorded during moderate to strong voluntary effort by leading off from many different regions of the muscle. With few exceptions, two to five atrophic muscles were examined from each subject. Intramuscular temperature was maintained at 36°C. as recorded

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*Working with a fellowship from the Rask-Ørsted Foundation.

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**Patients with poliomyelitis were not included in this study. They have been dealt with in a previous communication.[4]

TABLE 1

MEAN ACTION POTENTIAL DURATION IN NEUROGENIC ATROPHY OF PERIPHERAL AND SPINAL ORIGIN AS COMPARED WITH NORMAL

Action potentials in		*Number of muscles examined*	*Number of action potentials*	*Mean duration (in msec.)*	*Standard deviation (in msec.)*	*Mean error (in msec.)*
Normal muscle		12	410	5.85	1.9	0.09
Atrophies caused by peripheral nerve lesions		69	1,086	7.63	3.1	0.10
Atrophies caused by anterior horn cell lesions	mild	18	399	6.30	3.0	0.15
	severe	37	550	9.90	3.8	0.16

with an inserted thermocouple, by placing a heating pad over the muscle when necessary.

In every case, action potentials from two regions of the muscle were recorded simultaneously on the screen of a double beam oscilloscope. The duration, shape and amplitude of action potentials from involved muscles were compared with those from normal muscles, either the uninvolved symmetric muscles of the patient or the corresponding muscles of normal subjects matched for age.

The clinical degree of activity was classified on a six point scale from 0 (no activity) to 5 (normal activity).[5] Details as to this, and the detailed methodologic description of the electrodes, recording and amplifying procedure, determination of action potential parameters, and statistical treatment of the data have been published.[6,7] Muscle biopsy* was examined in most cases, and the degree of atrophic change agreed, on the whole, with the clinical estimate.

RESULTS

1. Action potentials in muscular atrophies of spinal origin.

Eighteen patients had clear signs of muscular atrophy of spinal origin. In 12 of these cases, the *mean duration of action potentials* was significantly increased to 70 per cent above normal (table 1) or, including polyphasic potentials, to 82 per cent (column 4, table 2). This is shown in the histogram of figure 1a, where all action potentials with a duration of more than 7 msec. are represented to a much higher degree than in normal muscle, those shorter than 7 msec. to a lesser degree.

Six of the 18 cases had a mean duration within normal limits (+8 per cent excluding (table 1) and + 26 per cent including polyphasic potentials, column 3, table 2). The corresponding histogram of figure 1b shows no systematic difference from normal muscle in the representation of action potentials of various durations.

*Our thanks are due to Dr. Erna Christensen, laboratory of neuropathology, Institute of Pathology, University of Copenhagen, for carrying out the histologic examinations.

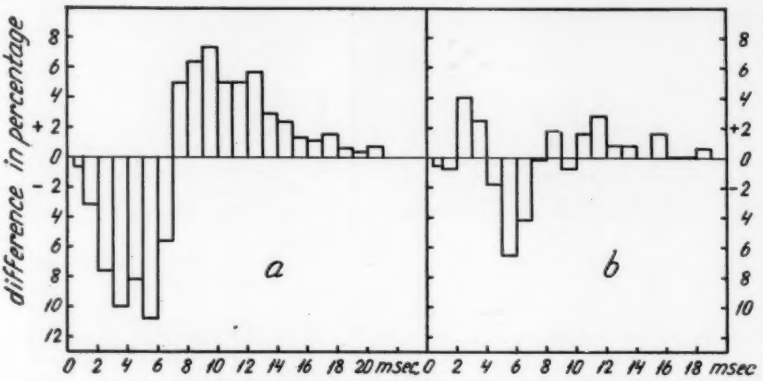
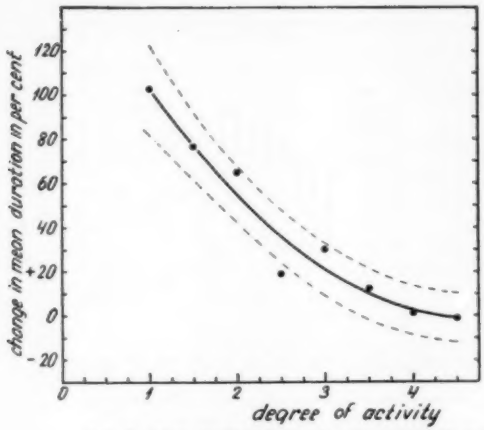


FIG. 1. Neurogenic atrophy of spinal origin. Distribution of mean action potential durations expressed as the difference between histograms of normal and atrophic muscle. a) 12 cases: muscles with increased mean duration and severe atrophy. ($N_2 = 550$, $N_1 = 401$). The columns below the zero line indicate the reduced occurrence of action potentials below 7 msec. Columns above the line indicate the increased occurrence of action potentials above 7 msec. as compared with normal muscle. b) 6 cases: muscles with normal mean duration and mild atrophy. ($N_2 = 399$, $N_1 = 401$). The distribution of durations shows that there is no systematic deviation from normal muscle. N_1 and N_2 denote the total number of action potentials in normal and atrophic muscles respectively.

The grouping on the basis of action potential duration coincides with the clinical degree of atrophy:[5] all muscles with a marked loss of activity (below 2,5) fell in the group with increased action potential duration (figure 1a, and column 4, table 2); all muscles with mild loss of activity (above 2,5) had a mean action potential duration within normal limits (figure 1b and column 3, table 2). There was, however, no correlation between the maximum number of recordable action potentials from a given area and the increase in mean action potential duration.

That the correlation between degree of atrophy and increase in mean action potential duration was quantitative as well, is shown in figure 2, where average mean duration is plotted against the degree of activity at maximum effort: the less the activity, the greater the action potential duration. Not only was this positive correlation statistical, it held in individual cases as well. An example is given in figure 3, showing histograms taken one year apart in a case of rapidly progressive amyotrophic lateral sclerosis. In the first examination, the degree of activity was estimated at 3,5 and the range of action potential durations was normal; it was displaced toward the side of long durations in the second examination after considerable progression of the disease, when the activity was estimated at 1,5.

In figures 4 and 5, examples are given from individual cases of the distribution curves of action potential durations, biopsies and slow speed electromyo-



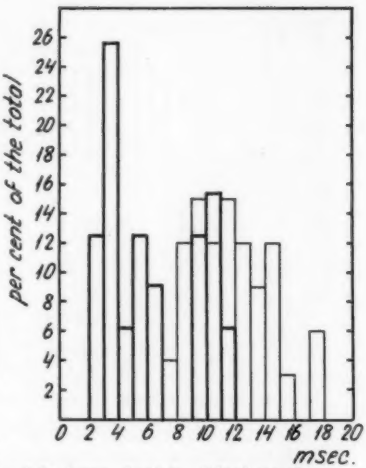


FIG. 2. Mean duration of muscle action potentials expressed as the difference in per cent between values in atrophies of spinal origin and normal muscle as a function of the degree of activity, defined according to M.R.C.5 Dashed lines indicate mean error. FIG. 3. Two histograms of action potential duration taken at a one year interval from the same muscle (biceps brachii sin.) in a case of amyotrophic lateral sclerosis. First examination (full lines) approximately normal values (mean duration 19 per cent above normal); second examination (thin lines) significant increase in duration (mean duration 75 per cent above normal). Each histogram represents 30 action potentials.

grams from the same muscle. They represent different degrees of atrophy of spinal origin. In figure 3, a case of amyotrophic lateral sclerosis in the initial stage, the atrophy was slight, there were clear indications of patchy atrophy on biopsy, and the mean action potential duration was normal. Only when the patchy atrophy was more generalized, as in figure 5, was there a significant increase in mean duration.

In the majority of muscles examined (35 of 52), the *mean amplitude of action potentials* exceeded that of normal muscle. There was no systematic correlation between amplitude and duration of the individual action potentials, with the exception that potentials of very long duration (>11-20 msec.) were preferentially represented amongst those with low amplitude. There was no certain correlation between increase in amplitude and degree of atrophy, but there was a tendency for high amplitude potentials to occur in the presence of moderate atrophy (degree of activity 2 to 2,5). The mean amplitude was lower in muscles with slight and severe degrees of atrophy.

The distribution of the *various shapes of action potentials* in severe spinal atrophy is shown in figure 6 and is compared with the corresponding distribution in normal muscle. As in normal muscle, the majority of action potentials was di- and triphasic. In contrast with normal muscle *polyphasic potentials* (more than four phases) were increased at the expense of the tetraphasic and were chiefly of the "grouped action potential" type with the spike duration of

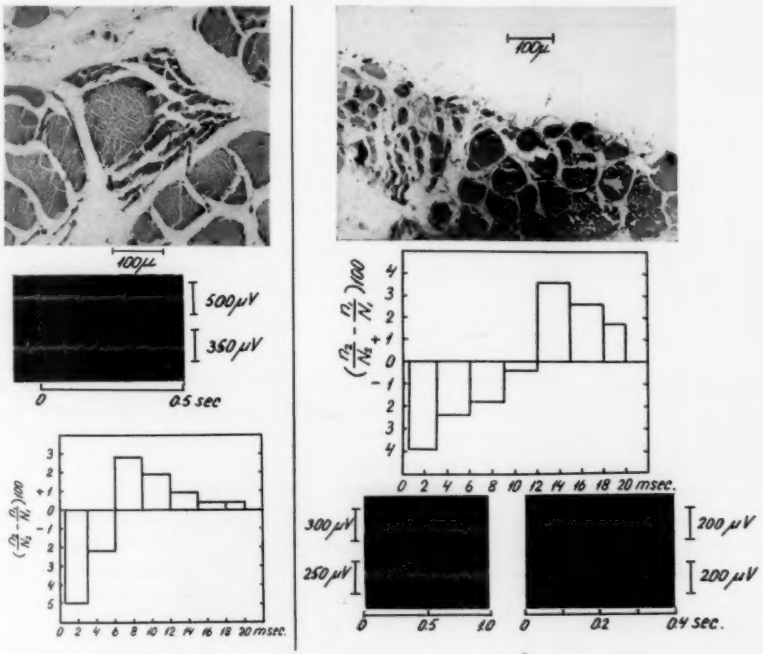


FIG. 4. Amytotrophic lateral sclerosis: biopsy, electromyogram and distribution curve of action potential durations of the left deltoid muscle. Male, 41 years old, first signs of the disease noticed six months ago, atrophy of all muscles of the hand, fasciculations. No sensory loss. The deltoid muscle was only slightly affected (degree of activity: 4). *Top:* biopsy with patchy atrophy. *Middle:* electromyogram recorded at slow speed, showing single oscillations during maximal effort. *Bottom:* difference between histograms of action potential duration in the atrophic and in normal muscle. The increase in the relative number of long potentials (columns above zero line) is so small that the change in mean duration is only 1 per cent above that of normal muscle. The mean action potential amplitude was 130 per cent above normal. Total number of action potentials in atrophic muscle $N_2 = 31$, in the corresponding normal muscle $N_1 = 115$. n_1 and n_2, relative number of action potentials per interval of duration. *abscissa:* duration in msec. *ordinate:* difference in relative number of action potentials per interval of duration between atrophic $(\frac{n_2}{N_2} \cdot 100)$ and normal $(\frac{n_1}{N_1} \cdot 100)$ muscle.

FIG. 5. Syringomyelia: biopsy, distribution curve of action potential durations and electromyogram from the left brachial biceps. Male, 22 years old, first signs of the disease six years ago, flaccid paresis of both legs, slight paresis of left arm and small muscles of the hand, thermoanesthesia of both upper extremities. *Above:* biopsy with signs of neurogenic atrophy. *Middle:* difference between histograms of action potential durations in the atrophic and the corresponding normal muscle. The negative part of the diagram expresses the decreased incidence of action potentials with short duration corresponding to an increase in mean duration. Total number of action potentials in the atrophic muscle $N_2 = 22$ and in normal muscle $N_1 = 225$. The mean action potential duration was 35 per cent above normal. *abscissa:* difference in the relative number of action potentials per interval of duration between atrophic $(\frac{n_2}{N_2} \cdot 100)$ and normal $(\frac{n_1}{N_1} \cdot 100)$ muscle. The mean action potential amplitude was 93 per cent above normal. *Below:* electromyograms recorded at low speed; *left*: maximal effort resulting in a transitory state.[1,2,7] *Right:* slight effort, single oscillations, synchronous in two leads.

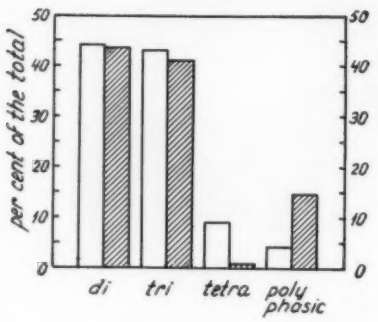


FIG. 6. Distribution of different shapes of muscle action potentials in severe spinal atrophy (hatched columns) and in normal muscle (white columns). Number of action potentials in normal muscle: 1799; in atrophic muscle: 835.

the normal triphasic potential. They occurred as 19 per cent of all potentials, as compared with 3 to 4 per cent in normal muscle, and were slightly more frequent in mild (23 per cent) than in severe (16 per cent) degrees of atrophy. Similarly, they occurred in all muscles with slight impairment of activity (>2,5) and in 60 per cent of muscles with severe atrophy (table 2). In spite of the increase in polyphasic potentials, the change in both duration and amplitude of action potentials was attributable chiefly to the increased duration and amplitude of the regularly shaped di- and triphasic potentials (figure 7c and d). Simple diaphasic and triphasic action potentials of long duration (>12 msec.) occurred in all muscles with moderate or severe atrophy.

TABLE 2

DIFFERENTIATION BETWEEN NEUROGENIC ATROPHY OF PERIPHERAL AND SPINAL ORIGIN

	Peripheral Origin		*Spinal Origin*	
	mild	*severe*	*mild*	*severe*
Total number of recorded action potentials	324	876	480	704
Number of polyphasic action potentials (per cent of all action potentials)	23	20	13	16
Muscles with grouped polyphasic potentials (per cent of muscles examined)	0	60	100	60
Mean action potential duration, including polyphasic potentials (per cent above normal)	46	44	26	82
Muscles showing simple action potentials longer than 12 msec. (per cent of muscles examined)		36		100
Mean action potential amplitude (per cent above normal)	7	4	102	119
Occurrence of fibrillation potentials (per cent of muscles examined)	13	45	64	55
Occurrence of fasciculation (per cent of muscles examined)	0	0	50	30

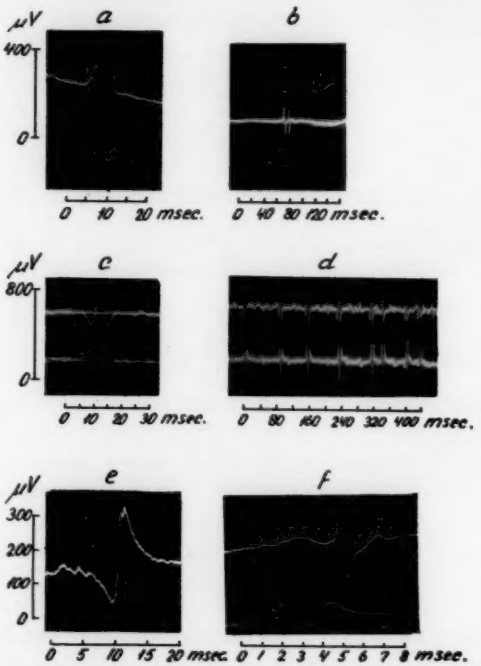


FIG. 7. Examples of action potentials in muscles with neurogenic atrophy recorded with concentric electrodes. a) fasciculation in spinal atrophy. b) as a) at slower recording velocity. c) triphasic action potentials of long duration and high amplitude dominating the spectrum of action potentials in spinal atrophies. d) as c), lower recording velocity, synchronous activity recorded with two separate leading off electrodes 2 cm. apart. e) peripheral nerve lesion, diphasic muscle action potentials, long duration, normal amplitude. f) triphasic action potentials of short duration and low amplitude as in normal muscle. The oblique x-axis in record is due to the slow moving of the film during the sweep time.[6]

The *spontaneous motor unit activity* of apparently relaxed muscle consisted of fasciculation and fibrillation potentials. The former, a characteristic feature of spinal lesions, consisted of polyphasic action potentials with four to five repetitive spike discharges of relatively high amplitude (figure 7a and b). Unlike the synchronous activity of different motor units accompanying voluntary activity in spinal atrophy, this spontaneous fasciculation was not synchronous over wide areas of the muscle. Even in "contraction fasciculation," i. e. voluntary contraction of parts of a muscle,[8] polyphasic action potentials were observed which were non-synchronous when led off simultaneously from two points of the active region.

Fibrillation action potentials have been described in muscular atrophy of spinal as well as of peripheral neurogenic origin.[9,10,11] In the present material, they occurred as often in spinal as in peripheral neurogenic atrophy, and in

TABLE 3

INCIDENCE OF FIBRILLATION ACTION POTENTIALS

Muscle atrophy caused by	Total number of muscles	Number of muscles showing fibrillation action potentials (duration 0,5 - 2 msec.)								mean degree of activity in muscles	
		total		duration of disease						with fibrillation	without fibrillation
				6 months		<5 years		>5 years			
		number	%	number	%*	number	%**	number	%***		
Lesions of the peripheral nerve	69	23	33	15	43	7	24	1	20	1,3	1,8
Affections of the anterior horn cells	51	21	41	3	23	12	57	6	35	2,0	2,7

* in per cent of all muscles from patients with duration of the disease <6 months
** in per cent of all muscles from patients with duration of the disease <5 years
*** in per cent of all muscles from patients with duration of the disease >5 years

spinal atrophies were found in later stages of the disease (one half to five years). Muscles with fibrillation showed a more severe disability than those without (table 3).

2. *Muscle action potentials in atrophies following peripheral nerve lesions.*

Of the 34 cases examined, 16 showed a statistically significant increase above normal in *mean action potential duration* (+50 per cent excluding polyphasic potentials). The remaining 18 cases had no statistically significant changes in mean action potential duration. In the group of peripheral nerve lesions as a whole the average increase in action potential duration was 30 per cent or, if polyphasic potentials were included, 45 per cent (table 1). Hence, the increase in mean duration, when present, was not caused solely by the increase in the number of polyphasic potentials; it was due mainly to an increase in the duration of regularly shaped di- and triphasic action potentials (figure 7e). The findings of action potential duration in individual cases were reproducible, as was shown by repeated examinations over periods as long as 20 weeks.

The changes in *mean action potential amplitude* were inconsistent, but the majority of muscles had a mean action potential amplitude within normal limits (table 2). There was no correlation between amplitude and duration. Polyphasic potentials were usually of high amplitude.

The distribution of different shapes of action potential was substantially the same as in atrophy of spinal origin (figure 6). Tetraphasic potentials were rare, and polyphasic potentials were increased to 22 per cent. They occurred equally in muscles with normal and in those with increased mean duration. The polyphasic potentials were mainly those with a short spike duration, as in 1 per cent of action potentials in normal muscle. "Grouped polyphasic potentials" occurred less frequently and, when present, were confined to muscles with severe atrophy (table 2).

In the present material of peripheral nerve lesions, *fibrillation* was found in

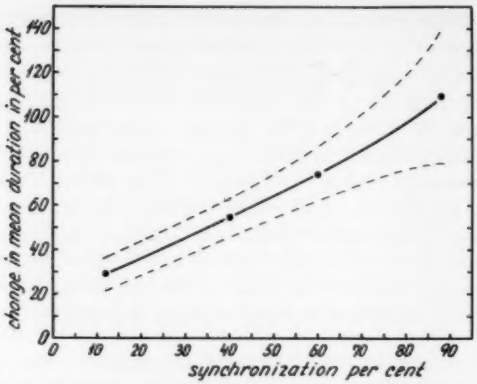


FIG. 8. Mean duration of muscle action potentials (expressed as the difference in per cent between values in atrophies of spinal origin and normal muscle) as a function of per cent coincident action potential. Dashed lines indicate mean error.

23 of 69 muscles examined or 30 per cent (table 3) and occurred when the disease had lasted less than half a year. Usually the spontaneous activity in the resting muscles was initiated by inserting the electrode, the repetitive firing lasting from one half to one minute. In a few cases, the fibrillation activity continued to appear during voluntary effort as well, but could easily be distinguished from the electrical responses accompanying the latter, since the frequency of fibrillation activity is not modified by changes in intensity of contraction.

Attempts to find a correlation between increased or normal duration and electromyographic or clinical features were unsuccessful. There was no correlation between the presence or absence of an increase in action potential duration and duration of the disease, type of peripheral nerve lesion or clinical or electromyographic evidence of atrophy. With respect to the latter, the degree of atrophy was likewise not correlated with the degree of increase in action potential duration including polyphasic potentials: the increase in mean duration amounted to 80 per cent in muscles with severe atrophy (degree of activity $<2,5$) and to 70 per cent in mild atrophy (degree of activity $>2,5$). There was no correlation between the change in mean action potential duration and the maximum number of recordable action potentials from a given area. Spontaneous activity (often present in totally or partially denervated muscle) was equally frequent in muscles with normal and with increased mean action potential duration.

There was, however, a correlation between degree of atrophy and the incidence of fibrillation. When fibrillation potentials occurred, the degree of paresis was more severe (degree of activity $= 1,3$) than in muscles which did not show fibrillation (degree of activity $= 1,8$) (tables 2 and 3).

3. Action potentials in muscle atrophies of combined peripheral and central neurogenic origin or of uncertain localization in the lower motor neuron.

In two cases of progressive neurospinal atrophy (Charcot-Marie-Tooth), the mean duration of action potentials was increased by 21 and 53 per cent.

In eight cases of polyradiculitis, findings varied according to the interval since the onset of the illness. In three cases, the onset of the disease was within a month of the examination and in these the action potential duration was normal in two and slightly increased in one. In five cases atrophy had been present between two months and 20 years; in all these at least one muscle showed a significant increase in mean duration (average in 13 muscles 100 per cent).

Three of four patients with uncertain localization of the lower motor neuron affection showed a significant increase in mean duration, while in one the increase was slight.

The distribution of different shapes of potentials was the same in cases of combined peripheral and central neurogenic origin as in servere spinal atrophy, exemplified in figure 6.

DISCUSSION

In the majority of cases examined, muscles with atrophy of neurogenic origin showed an increased mean duration of action potentials. In peripheral nerve lesions, this increase was associated with normal amplitude; in atrophies caused by affection of the anterior horn cells the amplitude was increased.

In several respects, the duration, shape and amplitude of action potentials in cases of spinal musclar atrophy differed from those of peripheral neurogenic origin. The differences are summarized in table 2.

a. In atrophy of peripheral neurogenic origin, action potential duration was not correlated with the degree of atrophy as evidenced clinically or by biopsy. In atrophy of spinal origin, on the other hand, the clear correlation between the degree of atrophy and the increase in action potential duration was quantitative, and valid not only statistically for the group as a whole but in individual cases as well.

b. Peripheral and spinal atrophies differed with respect to the occurrence of simple action potentials longer than 12 msec. Such long action potentials occurred in all muscles with moderate to severe atrophy of spinal origin (31 muscles). In peripheral nerve lesions with a corresponding degree of atrophy, they occurred in only 36 per cent (in 21 of 56 muscles).

c. The mean action potential amplitude in the majority of muscles with spinal atrophy exceeded that of normal muscle, whereas it was normal in peripheral neurogenic atrophy.

d. Polyphasic potentials of the "grouped action potential" type occurred more frequently in spinal atrophies than in those of peripheral neurogenic origin. The polyphasic potentials in peripheral neurogenic atrophy were chiefly of the short spike potential type.

e. Spontaneous activity in the form of fasciculation was confined to spinal atrophy, and was accompanied by polyphasic action potentials. Fibrillation

activity was observed equally in peripheral and spinal neurogenic atrophy, and in both it occurred more frequently in muscles with severe disability. In spinal atrophy, however, it occurred chiefly at a later stage of the disease, while in peripheral nerve lesions it occurred when the disease had lasted less than half a year. Assuming fibrillation to be an indication of denervation,[3,9,10,11,12] this difference is referable to differences in the onset of denervation which in cases of spinal localization need not coincide with the onset of the disease.

f. Synchrony occurred more frequently in spinal than in peripheral neurogenic atrophy. Synchrony is defined as the consistent concidence within 10 to 20 msec. of action potentials from two separate points of a muscle. Such coincidence occurred in 65 to 80 per cent of the points investigated in spinal atrophy; in less than 20 per cent in normal muscle and in atrophies of peripheral neurogenic origin.[1,13,14]

In discussing factors which could account for the changes in action potential duration and amplitude, it is well to be clear that the disease process destroys some motor units, and that the changes in action potential parameters are recorded from surviving motor units. At present, it is hardly possible to give an interpretation which applies both to spinal and peripheral neurogenic atrophy. In both instances the changes in muscle action potential parameters must be attributable to affection of the lower motor neuron. When the upper motor neuron alone is involved, the action potential duration is normal.

In cases of spinal atrophy, the effects of involvement of surviving anterior horn cells are such as to provide a plausible explanation for the increase in action potential duration and amplitude. It has already been shown that, in such cases, motor units from different parts of the muscle tend to discharge synchronously, and there is an increase in amplitude of the individual action potentials.[2,13,14] A slight phase displacement of these discharges could account for an increase in duration of the resulting action potentials, as is discussed more fully in connection with experimental nerve block.[16] It is in favor of this explanation that, in cases of spinal atrophy, there existed a clear correlation between the increase in mean action potential duration and the degree of synchrony (figure 8). The synchronization in these cases occurred both at slight and at strong voluntary effort, but was accentuated at maximum effort. The synchronizing effect of strong effort in normal muscle[15] is accentuated in paretic muscle in which maximum effort is more readily attempted. The occurrence of grouped polyphasic action potentials with spikes of the same duration as the normal spike can also be considered an indication of an increased tendency toward synchronization of fibers from different motor units.[16]

The increased action potential duration observed in atrophies of peripheral neurogenic origin is distinguished in several respects from that of spinal origin and must be explained on a different basis. The distinguishing features are: that it occurred less frequently; that it was not associated with an increase in amplitude; and that it was not correlated with the degree of atrophy. Tentative explanations for the increased duration in peripheral neurogenic atrophy may be offered:

a. In a partially denervated muscle the amount of inactive tissue will increase. Therefore, the relative mean distance between electrode and active fiber will be larger than in normal muscle, and, muscle being a volume conductor, this will result in an increase in duration. Similar effects can be observed in normal muscle, when comparing the duration of action potentials led off with intramuscular and subcutaneous electrodes.[17] If this were a full explanation one would expect that the increase in mean duration would increase with increasing atrophy. There was, however, no such correlation.

b. Assuming that action potentials of long duration generally are the result of a slightly out-of-phase activity of several fibers belonging to the same subunit, the higher mean duration could be due to an increase in the number of fibers belonging to it. Evidence has been provided that recovery in lower motor neuron affections may occur by peripheral outgrowth of axon branches.[18–22] Thereby the number of fibers belonging to the same motor unit would be increased. However, this factor can hardly account for increases in duration which have been observed as early as 15 days after the onset of the disease.

c. An increased temporal dispersion in the activation of the different muscle fibers belonging to the same subunit could explain the increase in duration found in peripheral nerve lesions. However, a decrease in conduction velocity[23] over the short intramuscular nerve branches could not vary over intervals large enough to account for the large changes in action potential duration. Variations in end plate delay could, on the other hand, cause a large increase in temporal dispersion of the activation of different fibers.

d. A decrease in propagation velocity of the wave of excitation over the muscle fiber would account for an increase in duration. An assumption of changes of this type is not purely hypothetical in view of the increased duration in the muscle fiber action potential observed in animal experiments after application of adrenalin.[24] Speculations as to whether changes in vegetative innervation could actually cause the changes in mean action potential duration would lie beyond the scope of this paper.

Explanations c. and d. seem the most plausible of those offered and are in addition consistent with the observed normal action potential amplitude in peripheral neurogenic atrophy, and with the increased occurrence of polyphasic potentials, especially those with short spike duration.

SUMMARY

Duration, shape and amplitude of muscle action potentials recorded during voluntary effort have been studied in 67 cases of muscular atrophy of neurogenic origin.

In most cases (60 per cent) with *atrophies caused by involvement of the anterior horn cells* there was an increase in both mean duration and amplitude of the action potentials. This increase was the more pronounced the more advanced was the stage of the disease, and there was a significant increase in all cases with marked atrophy (figures 1 and 2). A correlation was found in these cases between the mean duration of action potentials and the degree of syn-

chronization of action potentials from different motor units (figure 8). In view of this finding, it seemed possible that a slight temporal dispersion of nearly coincident discharges from *different* subunits might account for the increase in duration of the action potentials in spinal atrophy. This view is consistent with the finding of an increased action potential amplitude in these cases.

In *atrophies caused by peripheral nerve lesions,* a statistically significant increase in mean duration was found in 16 of 34 cases and was generally associated with normal mean amplitude of action potentials. The presence of an increase in mean duration was not correlated with the severity or the duration of the disease, nor were the cases with normal action potential parameters different in any way from those with alterations. Possible explanations for the increased duration and the normal or decreased amplitude of muscle action potentials in peripheral nerve lesions are discussed. It seems most plausible to assume an increase in temporal dispersion of the activation of fibers within the *same* subunit, due to changes in end plate delay or impulse propagation over the muscle fiber.

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Studies in Neuromuscular Diseases with Radioactive Potassium

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Frequent observations of the profound muscle weakness associated with potassium depletion following diabetic coma and the striking effects of potassium administration in certain cases of familial periodic paralysis emphasize its important role in normal muscle function. Recent work by Cannon[1] has shown the essential nature of potassium in the synthesis of muscle protein and the failure of this tissue to develop in depleted animals. Furthermore, the inability of muscle to phosphorylate creatine in the absence of potassium has been known for some time and is another indication of its fundamental importance in muscle metabolism.[2]

The determination of serum potassium in the various neuromusclar diseases has been of no help to the clinician or the investigator, for the values obtained have been almost uniformly within the normal range. Since 95 per cent of the body potassium is intracellular, it is evident that in most instances serum values do not adequately reflect intracellular derangements of potassium metabolism. It seems apparent, therefore, that the approach to this problem at the clinical level must be necessarily indirect and cannot be based upon determination of serum potassium alone.

The availability of artificial isotopes of biologically important elements in recent years has made possible the study and measurement of elements such as potassium in the living human body. In this study, an attempt was made to investigate the distribution and metabolism of potassium in various neuromuscular diseases using radioactive K^{42}. The isotope dilution technique was used to determine the total body exchangeable potassium.

Exchangeable potassium is an index of the total body potassium, excluding that small component contained in the erythrocytes, bones and brain, repre-

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senting a maximum of 5 per cent.[3] For all practical purposes, therefore, the value obtained for exchangeable potassium may be considered a good indication of total body potassium and particularly muscle potassium, since more than 70 per cent of the body's potassium is contained in the muscle cells.

PROCEDURE

Radioactive K^{42} was administered to 28 patients with neuromuscular diseases and to eight normal subjects. Fifteen patients had progressive muscular dystrophy and seven had myotonia dystrophica. In both of these groups there was a wide range in severity and degree of disability of the individual cases. Three cases of progressive muscular atrophy were also studied. Two showed advanced disease and one only minimal manifestations. The last group included three individuals with severely disabling residuals following bulbospinal poliomyelitis.

The radioactive K^{42} was given orally, with three exceptions when it was administered intravenously. Exchangeable potassium was determined by isotope dilution according to the method described by Corsa and co-workers.[3] All radioactive materials were counted in liquid state with a thallium-activated sodium iodide crystal scintillation counter.[4] In addition, 24 hour creatinine excretion was measured in most subjects.

TABLE 1

		Creatinine		*Potassium*	
	Cases	*Gm./24 hr.*	*Mean -S.D.*	*Ke meq.*	*Mean -S.D.*
Control	8	1.23-1.51	1.34 ± 0.13	2900-3500	3160 ± 253
Muscular dystrophy	15	0.24-1.26	0.75 ± 0.30	800-2700	1932 ± 602
Myotonia dystrophica	7	0.6 -1.2	1.04 ± 0.24	1700-2800	2177 ± 419
Muscular atrophy	3			1500-2600	
Post-polio (Bulbospinal)	3	0.7		1200-1500	

RESULTS

The results of this study are summarized in table 1. The values obtained for the control subjects ranged from 2900 to 3500 meq., with a mean of 3160 meq. These correlate well with the results obtained by Corsa and co-workers, using the oral route of K^{42} administration.[3] The muscular dystrophy patients had exchangeable potassiums ranging from 800 to 2700 meq., with a mean of 1932 meq. The exchangeable potassium of the seven patients with myotonia dystrophica ranged from 1700 to 2800 meq., with a mean value of 2177 meq. Several patients with primary neurone disease also showed markedly depressed exchangeable potassium levels, particularly the three patients with marked residual disability following bulbospinal poliomyelitis.

The 24 hour creatinine excretion of the patients with muscular dystrophy and myotonia dystrophica were significantly diminished with mean values of 0.75 gm. and 1.04 gm., respectively.

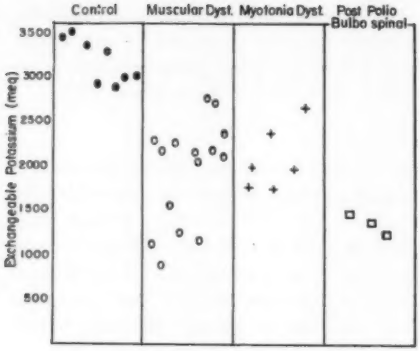

FIG. 1. Distribution of the exchangeable potassium values in various neuromuscular diseases.

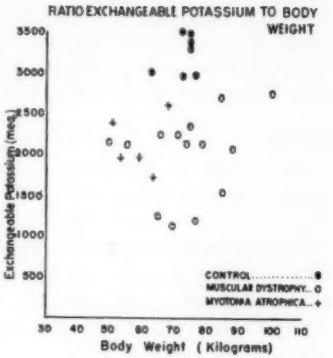

Fig. 2

The actual distribution of the exchangeable potassium determinations in these cases is better seen in figure 1. Here it is readily apparent that despite the wide range of exchangeable potassium in patients with muscular dystrophy and myotonia dystrophica, there is actually very little tendency for these values to overlap the control range. The bulk of the values obtained in such cases are well below the control levels.

In all patients under study, the serum potassium was within normal limits.

DISCUSSION

In the cases studied, the degree of impairment of muscle function was directly related to the level of exchangeable potassium. Those individuals having exchangeable potassium above 2500 meq. had very little disability. Levels of 1800 to 2500 meq. included patients with moderately advanced muscle wasting, and those below 1800 meq. were severely disabled.

In the normal individual, body weight is an approximate index of body potassium; however in the patients with muscular dystrophy and myotonia dystrophica, there was no correlation between body weight and the exchangeable potassium. From figure 2, it is readily apparent that many patients having relatively similar body weights exhibit a wide range of exchangeable potassium values. The controls, however, show a good correlation between exchangeable potassium and body weight.

The results of this study strongly suggest that there is positive correlation between: 1) total body potassium, 2) the degree of muscular disability, and 3) the 24 hour creatinine excretion. The correlation between exchangeable potassium and the 24 hour creatinine excretion is shown in figure 3. The data plotted in this way may be grouped arbitrarily according to the degree of pathologic involvement. In general, those cases falling into the group designated as 1+ showed little if any disability and relatively high exchangeable potassium and

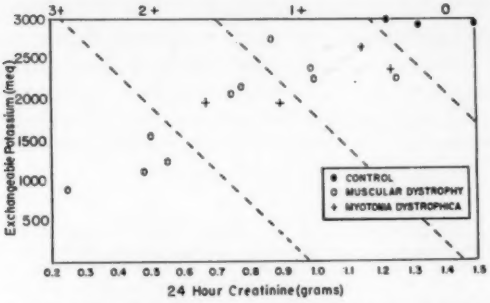

FIG. 3. Correlation of exchangeable potassium with 24 hour creatinine excretion and the degree of pathologic involvement.

creatinine excretion values. In the next group designated 2+, patients with moderately advanced disease are indicated. The exchangeable potassium and creatinine excretion were correspondingly diminished in these cases. In the last group, 3+, are patients with severe muscular involvement and complete disability. Here both exchangeable potassium and creatinine excretion are markedly depressed.

Of particular interest are the cases in the first group. The muscular dystrophy patients in this group exhibited only slight muscular weakness not readily apparent to the casual observer. The only stigma exhibited by the patients with myotonia falling into this category was the myotonic reflex. Nevertheless, despite the minimal clinical involvement and a normal creatinine excretion, the exchangeable potassium in every one of these cases was significantly depressed.

It would appear from these studies that exchangeable potassium may be a more sensitive index of early or incipient muscular dystrophy and myotonia dystrophica than is creatine or creatinine excretion. Exchangeable potassium values were found to be depressed in three cases of muscular dystrophy and two cases of myotonia dystrophica, having only subclinical or minimal manifestations. In severe neuromuscular disease, however, both exchangeable potassium and creatinine excretion were markedly depressed and in general the level of exchangeable potassium corresponded to the degree of disability.

The fact that there are diminished stores of potassium in the diseases under study has not been explained. One cannot state with any degree of certainty whether this is responsible for or simply a manifestation of the underlying disease. The possibility of an inherent intracellular metabolic defect, causing a gradual leakage of potassium from the cells and an intractably negative potassium balance, is suggested by the finding of diminished potassium values in subclinical or minimal muscular dystrophy cases. This aspect of the problem is now under investigation.

SUMMARY

In this study an attempt was made to investigate the distribution and metabolism of radioactive potassium in neuromuscular diseases. The isotope dilution technique was used to determine total body exchangeable potassium.

The results indicate a marked diminution of the exchangeable potassium in muscular dystrophy and myotonia atrophica, actually preceding the development of significant clinical findings in several cases.

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Megrim, and especially the form known as "sick-headache," is almost universally regarded by the patients themselves, as well as by medical practitioners, as an incurable malady. I am constantly told by those who consult me for other complaints that they have suffered all their lives from these headaches, adding, "But it is not for that I want your advice," or "I know that you cannot do anything for that." Mr. B. said that he had "never derived any good from medicine;" W. R., "no permanent benefit;" S. A., "no relief from medicine," and so on. It was the same in the time of Drs. Fothergill and Heberden; the former observes of the sufferers from sick-headache that, "wearied perhaps with ineffectual endeavours they at length give up all hopes of getting rid of their malady, and think patience must be their only cure." Of that form which consists in transient half-blindness followed by headache, Dr. Heberden says, "I have never been able to discover any remedies either for their cure or relief;" and he afterwards observes of such headaches in general, "I have noticed in numberless instances that they almost always become milder, and generally vanish towards the decline of life. This consideration must supply the place of a remedy where every other fails; for it is some consolation for a man to know, that if he cannot cure his distemper, he will nevertheless have a good chance to outlive it. This is likewise true of that headache mentioned among the diseases of the eyes, which begins with a mist before the sight." Similar views prevail on the Continent. "L'art impuissant a guerir la Migraine" – such, says Labarraque, is the objection commonly urged against all attempts to remedy this malady.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Relationship of Homologous Brain Proteolipid to Allergic Encephalomyelitis in Guinea Pigs

Norman P. Goldstein, M.D., Lawrence C. Kolb, M.D., Harold L. Mason, Ph.D., George P. Sayre, M.D. and Alfred G. Karlson, Ph.D.

EXPERIMENTAL allergic encephalomyelitis is a disease which has been produced in animals by the subcutaneous injection of heterologous or homologous brain tissue. Both clinically and pathologically it is similar to the encephalitides following rabies vaccination and smallpox vaccination and to the encephalitis following acute infections such as measles, mumps and whooping cough. The pathologic picture shows both inflammatory and degenerative lesions in the central nervous system.

While many inconclusive efforts had been made to demonstrate that brain tissue injected parenterally caused lesions in the central nervous system, Rivers, Sprunt and Berry[1] demonstrated in 1933 an encephalomyelitic lesion produced in monkeys by injections of brain emulsion and an alcoholic solution of brain given over a period of many months. In 1942, Freund and McDermott[2] advocated the use of an adjuvant consisting of a mixture of aquaphor, mineral oil and killed tubercle bacilli, to enhance the sensitization of guinea pigs to injection of foreign proteins. Since that time there have been many papers dealing with the rapid production of an allergic encephalitis in guinea pigs using either heterologous or homologous brain combined in this mixture. A number of workers have attempted to isolate and identify chemically the encephalitogenic factor in brain. The most recent and productive investigation along these lines has been carried out by Olitsky and Tal[3–5] who reported that a mixture of proteolipid A and B contained or was the factor responsible for the production of acute encephalomyelitis in mice. We might mention that the substances known as proteolipids are a group of lipoproteins isolated by Folch and Lees.[6] The proteolipids differ from the known lipoproteins inasmuch as they are insoluble in water but soluble in a chloroform-methanol-

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water mixture. The proteolipids, like lipoproteins in general, consist of a lipid and a protein component.

The purpose of this paper is to report on our investigations which represent an extension of knowledge on the relationship of brain proteolipids to experimental allergic encephalomyelitis.

METHODS AND MATERIALS

Sterile glassware and materials were used to prepare a Freund adjuvant-brain mixture by the method described by Kabat and associates.[7] Nine parts of freshly removed guinea pig brain were mixed for three minutes in a Waring blendor with 10 parts of 0.85 per cent solution of sodium chloride containing 0.5 per cent phenol. To this mixture were added 10 parts of aquaphor, which had been melted in a water bath, and 20 parts of liquid petrolatum containing 2.5 mg. of dead tubercle bacilli per milliliter. The ingredients were again mixed for about three minutes in the blendor and the resulting material was transferred to flasks and heated at 60° C. for one hour.

One milliliter of this mixture was injected subcutaneously over the sternum into male guinea pigs weighing approximately 700 gm. each. These groups of animals which were injected with the whole brain-Freund adjuvant made up our control series.

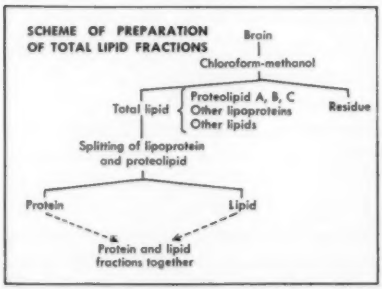

FIG. 1. Scheme of preparation of total lipid fractions.

For the experimental part of this work, total lipid fractions and proteolipid fractions from the brains of normal guinea pigs were substituted for the whole wet brain in the Freund adjuvant mixture. The amount of lipid material was approximately that derived from the standard weight of brain. The total lipid fractions were prepared according to the method of Folch, Ascoli, Lees, Meath, and LeBaron[8] (figure 1) while the proteolipid fractions were prepared according to the method of Folch and Lees[6] (figure 2).

Following injection of the brain or lipid mixtures, all animals were examined on alternate days for evidence of paralysis. The brains and spinal cords were preserved from all animals that died during the study and from those that were killed at the conclusion of the period of observation varying from

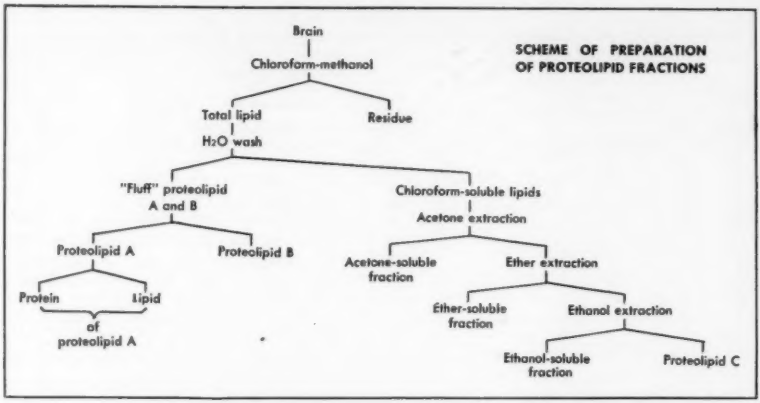

FIG. 2. Scheme of preparation of proteolipid fractions.

46 to 66 days after injection. The severity of lesions in the central nervous system was graded from 1 to 4 depending upon the degree of changes. These varied from perivascular and meningeal cellular infiltration to necrotic lesions in the brain and cord (grade 4).

RESULTS

Eight groups of control animals injected with the whole brain-Freund adjuvant mixture were studied at different times over the course of a year. Of the total of 80 animals in this control series, 96 per cent had histologic changes in the central nervous system typical of encephalomyelitis while 86 per cent showed clinical evidence of paralysis. The consistency and duplication of results, both pathologically and clinically, should be noted in the various separate series of animals injected with the whole brain mixture (table 1).

In comparison with the encephalitogenic activity of whole brain, it was evident that the activity of total lipid from guinea pig brain or its fractions was much diminished. However, as can be readily seen from table 2, the total lipid fractions, which include lipoproteins, the protein fraction of the total lipid, and the combined protein and lipid fractions of the total lipids, do contain the encephalitogenic factor. The lipid fraction of the total lipid, on the other hand, showed very little activity. The results indicated that an active component of brain lipid is contained in the protein component of a lipoprotein found in the central nervous system.

A study of the encephalitogenic activity of the various brain proteolipids is presented in table 3. It is evident that of the three proteolipids, A, B and C, only proteolipid A contains significant amounts of the active factor. Proteolipid B and proteolipid C demonstrated little activity in comparison with proteolipid A. When proteolipid A was split into its respective protein and lipid components, there was a marked diminution in activity; each component was

TABLE 1
CONSISTENCY OF PRODUCTION OF ISOALLERGIC ENCEPHALOMYELITIS IN GUINEA PIGS

Group	Animals	Histologic changes in central nervous system		Paralysis		Died spontaneously	
		No.	Per cent	No.	Per cent	No.	Per cent
A	10	10	100	8	80	4	40
B	8	8	100	7	87	6	75
C	10	10	100	7	70	4	40
D	10	10	100	10	100	6	60
E	16	15	94	13	81	12	75
F	8	8	100	7	87	4	50
G	10	9	90	10	100	2	20
H	8	7	87	7	87	5	63
Total	80	77	96	69	86	43	54

found to have much less activity as an encephalitogenic agent than the complete proteolipid A.

It is of importance to note that the ether-soluble fraction remaining after extraction of all proteolipids from the brain also showed considerable encephalitogenic activity. In fact the lipid which is soluble in ether seems to equal proteolipid A insofar as the results are approximately equal. This activity demonstrated in the ether fraction cannot be ascribed to a proteolipid since

TABLE 2
COMPARISON OF TOTAL LIPID FRACTIONS WITH WHOLE BRAIN

Group	Animals	Histologic changes in central nervous system		Paralysis		Mortality	
		No.	Per cent	No.	Per cent	No.	Per cent
Whole brain controls	80	77	96	69	86	43	54
Total lipid	10	5	50	6	60	0	0
Protein fraction of total lipid	10	5	50	5	50	1	10
Lipid fraction of total lipid	10	1	10	1	10	0	0
Combined protein and lipid fractions of total lipid	10	6	60	6	60	0	0

during the process of lipid extraction from the brain, presumably all the active proteolipids have been removed prior to extraction with ether. On the other hand, a similar acetone-soluble fraction and an alcohol-soluble fraction show no encephalitogenic potency.

Our work also demonstrates that the usual single extraction with a chloroform-methanol solution, according to the technic of Folch and Lees, does not remove all the encephalitogenic factors from the guinea pig brain. The supposedly lipid-free protein residue remaining after extraction with chloroform-methanol showed considerable antigenicity. However, this activity is largely removed by triple extraction of the brain with the chloroform-methanol solution of Folch and Lees. It is probable that further extraction with chloroform-

TABLE 3
COMPARISON OF PROTEOLIPID FRACTIONS WITH WHOLE BRAIN CONTROLS

Group	Animals	Histologic changes in central nervous system		Paralysis		Mortality	
		No.	Per cent	No.	Per cent	No.	Per cent
Whole brain controls	80	77	96	69	86	43	54
Proteolipid A and B	6	3	50	5	83	0	0
Proteolipid A	14	8	57	10	71	1	7
Protein of proteolipid A	14	1	7	3	21	0	0
Lipid of proteolipid A	14	4	29	3	21	1	7
Proteolipid B	14	1	7	5	36	0	0
Proteolipid C	14	2	14	4	29	1	7
Acetone fraction of proteolipid	6	0	0	0	0	0	0
Ether fraction of proteolipid	14	7	50	8	57	0	0
Alcohol fraction of proteolipid	6	0	0	0	0	0	0
Residue of proteolipid extraction	20	8	42*	15	75	9	45
Triple-extracted residue	10	1	10	2	20	0	0

*Based on 19 cases. The brain and spinal cord of one animal in this group were lost.

methanol would remove all of the encephalitogenic factor from guinea pig brain.

COMMENT

In general, our work is in agreement with the majority of previous investigations insofar as we find that the encephalitogenic factor or factors are probably lipids which are soluble in a chloroform-methanol mixture and in ether. The lipid-free protein residue after triple extraction with chloroform-methanol solutions is practically free of the antigen responsible for allergic encephalitis. This work is in accord with the results of Olitsky and Tal who likewise showed that the "antigen" can be completely removed from the brain by extraction with a chloroform-methanol solution. It might be pointed out that our results and the results of Olitsky and Tal are in contrast with the previous work of Koprowski and Jervis[9] who found that the chloroform-methanol-soluble lipid fraction and the protein fraction after extraction were equally potent. In addition, the use of chloroform-methanol extraction provides a more potent "antigen" than the acetone-ether extraction of Ferraro and associates[10] inasmuch as their protein residue from the extraction of brains was more active than the lipids extracted with the acetone-ether mixture.

Our results are also essentially in agreement with those of Olitsky and Tal who found that the mixture of proteolipid A and B contained an encephalitogenic factor. However, we have shown that the activity of the proteolipid A and B mixture is due principally to the presence of the proteolipid A. Both proteolipid B and proteolipid C have little if any encephalitogenic potency. Our data suggest that the complete proteolipid A is necessary for the production of encephalomyelitis inasmuch as splitting the proteolipid A into its component protein and lipid fractions markedly reduces the encephalitogenic activity. Also the protein fraction prepared from the total lipid of

guinea pig brain may be another factor responsible for the production of encephalomyelitis. It is known that, in general, lipoproteins are soluble in ether and perhaps the antigenic factor found in our ether solutions and the protein split from the total lipid of the brain represent the same substance.

At this time the inference is made that there are two or more "antigens" in the brain which are the substances responsible for the production of allergic encephalomyelitis. One "antigen" would be considered as the proteolipid A of Folch and Lees while a second "antigen" might be the lipoprotein found in the ether fraction after removal of the proteolipids. This lipoprotein could conceivably owe its encephalitogenic activity to the protein fraction. If this is the case, it is possible that it is the same factor recovered in the protein fraction remaining after splitting the total lipids into the respective protein and lipid fractions. Thus, while previous investigations have suggested that the encephalitogenic factor is either a lipid or a protein, our results indicate that both views are presently tenable inasmuch as we have been able to produce encephalomyelitis in guinea pigs using either a proteolipid (A), a protein (separated from the total lipid of brain) or a lipid (the ether-soluble fraction derived during the preparation of the proteolipids).

SUMMARY

An investigation of the activity of brain proteolipids in the production of allergic encephalomyelitis has been carried out. Proteolipid A has been found to be the most active of the proteolipids in the production of encephalomyelitis. When proteolipid A is split into its component protein and lipid fractions, its activity is markedly decreased. Following extraction of proteolipids from whole brain, another encephalitogenic factor has been found which is soluble in ether. Finally a protein, isolated from the total lipid of the brain, is also capable of inducing experimental allergic encephalomyelitis in guinea pigs.

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CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by D. Denny-Brown, M.D. and J. M. Foley, M.D.

CASE PRESENTATION

A 28 year old man was admitted to another hospital on March 13, 1951 because of fits and unconsciousness of 45 minutes duration. On the day prior to his admission he complained of chilly feelings, headache, and chest pain, and reported to the physician at his place of employment. He was found to have a slightly elevated temperature and was sent home. Three-quarters of an hour prior to his admission, his wife found him convulsing and brought him directly to the hospital.

Past history: In April 1945, while in Germany with the Army, he developed slowly progressing stupor, with headaches, nausea, vomiting and diplopia. A diagnosis of brain tumor was made and he was transferred to an Army hospital. Investigation there revealed some chest abnormalities as well, and biopsy of a supraclavicular node yielded the report "Hodgkin's paragranuloma." Radiation was given to the chest and head (amount and physical factors not available).

Except for occasional severe headaches he got along well until February 1947 when he had a seizure. This began in the left hand and progressed to involve all extremities. The frequent recurrence of such seizures led to his admission to a Naval hospital in August 1947, where he was given a course of radiation to the head. During the radiation treatments he developed a partial paralysis of his right lower facial muscles, but this cleared after a few weeks. In addition to the seizures described above, he developed six to eight attacks a day in the course of which he stared into space, ceased all activity, and was oblivious to his surroundings. Later he had no memory of such episodes. At times he put his clothes on backwards. Tridione was given for these attacks but the frequency of grand mal attacks increased so alarmingly that this drug was discontinued.

His seizures continued every three or four months, and in 1949 he noted "dancing lights" prior to the convulsions. He remained well otherwise and was able to work.

In April 1950, during the course of an upper respiratory infection, he had a much more severe attack than usual. He was admitted to the Boston City Hospital. A lumbar puncture done at this admission showed an initial pressure of 140 mm., 8 lymphocytes, negative Pandy, total protein of 43 mg. per cent, and a gold sol of 122211100. The blood and cerebrospinal fluid Hinton were negative. After discharge he had no further seizures until the present illness, except for occasional "staring spells."

Physical examination: Temp. 107° F. Pulse 160. Blood pressure 70/30. The patient was slightly obese. He was convulsing almost continually when first seen, and there were clonic movements of both arms and legs. The seizures lasted three to five minutes, and recurred after 30 seconds. During these brief intervals of freedom from seizures, the arms were held in semiflexion and the legs in extension. The eyes were closed

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and the jaws clenched; the patient was very cyanotic and there was a pink froth coming from his mouth and nose.

The left pupil was dilated and neither pupil reacted to light. The optic fundi were natural. No reflexes were obtainable.

No skin rash or adenopathy was found. The lungs were clear, the heart was not enlarged. The abdomen was negative except for the liver which was palpable two fingers below the costal margin.

A mouth gage was put in place and administration of nasal oxygen was started. Suction was used frequently. Fifteen minutes after admission he was given 3¾ gr. of sodium Amytal intravenously, with prompt cessation of seizures. Carotid sinus pressure failed to slow the heart rate. An electrocardiogram showed only auricular tachycardia. Sponging with ice and alcohol failed to reduce the temperature, which remained at 107° F.

Although free of seizures for the next two hours, he remained unconscious. Seizures started again with clonic jerkings of the right arm, followed in a few minutes by less intense clonic movements of the left arm. These became generalized and lasted for five minutes after which he was given 5 gr. of sodium Luminal.

Respirations ceased shortly after this. Heart sounds became slow, faint, and irregular, and he expired, two and a half hours after admission to the hospital.

CLINICAL DISCUSSION

DR. DENNY-BROWN: In April 1945, while in Germany with the Army, the patient developed slowly progressing stupor, with headaches, nausea, vomiting and diplopia. It is assumed that this patient had increasing intracranial pressure. The further assumption seems to have been made that since there was a lymphadenopathy reported to be Hodgkin's paragranuloma by biopsy, there was mediastinal paragranuloma and cerebral Hodgkin's disease. But several questions arise immediately, first whether brain tumor caused the increased intracranial pressure. Though the patient had increased intracranial pressure and damage to one or more cranial nerves, it will be noted that there was no sign relating to damage of the brain itself. The way in which Hodgkin's disease ordinarily affects the nervous system is by extension to the extradural spaces. In that manner compression of the spinal cord is commonly caused, and occasionally extradural deposits in the skull damage cranial nerves. We therefore suspect that the diplopia was arising from some cranial extradural deposit rather than from cerebral metastasis. But what of the headache, nausea and vomiting? If the extradural deposit was large enough, it would displace the intracranial contents, or it could occlude one or more venous sinuses. But another difficulty is that we are told the biopsy showed paragranuloma, and this, being the most benign form of Hodgkin's disease, doubtfully if ever affects the central nervous system at all, according to Jackson and Parker[1] and Sparling, Adams and Parker.[2] If Hodgkin's disease does affect the nervous system, it is by the extradural extensions of either Hodgkin's granuloma or Hodgkin's sarcoma. There are cases on record of primary Hodgkin's sarcoma of the brain, but they are found primarily in the cerebellum, curiously enough without evidence of lymphadenopathy. There are reports of reticulum cell sarcoma occurring primarily in the temporal lobe, but in these cases there was also no lymphadenopathy. Since there was a presumed mediastinal mass with affection of lymph nodes, we must conclude that Hodgkin's granuloma was the probable pathology and that an extradural deposit in the skull was the cause of the cranial symptoms. The only explanation of the biopsy report is that the gland section by chance showed a more benign appearance leading to diagnosis of paragranuloma.

Except for occasional severe headaches, the patient got along well until February 1947 when he had a seizure. This began in the left hand and progressed to involve all extremities. The

frequent recurrence of such seizures led to his being given a further course of radiation to the head in August 1947. During the radiation treatments he developed a partial paralysis of his right lower facial muscles, possibly due to swelling of the parotid gland, since this cleared after a few weeks. His seizures persisted, however, and now developed features which clearly pointed to a temporal lobe focus. He developed six to eight attacks a day, with staring followed by confusion.

The attacks began in the left hand, and the staring followed by confusion was the "dreamy state" of temporal lobe epilepsy. Such an attack may be preceded by an abnormal odor or it may be associated with visual hallucinations, but the absence of these does not lessen the significance of the "dreamy state" which is a temporal lobe attack. The visual aura appeared later in 1949, and was of the poorly organized type associated with posteriorly placed lesions. That the patient was given Tridione indicates that the seizures were considered to be petit mal. Whatever his electroencephalographic findings may have been, the most important differentiation in relation to all epilepsy is that between focal epilepsy and general epilepsy, an attack beginning locally or beginning generally. A focal onset means a focal pathology. If a patient stares into space, ceasing all activity for a number of minutes, he is not suffering from petit mal. It seems quite obvious that this patient was suffering from focal epilepsy. I doubt whether the seizures were related to recurrence of cranial tumor. There is no further mention of headache, nausea, vomiting or diplopia.

In April 1950, he had a much more severe attack than usual in the course of an upper respiratory infection. He was admitted to the Boston City Hospital, and I remember seeing him at that time. We could find at that time no evidence of damage to the brain except focal right temporal lobe epilepsy and a few lymphocytes in the spinal fluid. It was suggested that scarring of the temporal lobe was the cause of the attacks. This impression was confirmed by a pneumoencephalogram which showed a dilated lateral ventricle on the right side. We could find no evidence of lymphadenopathy in chest, neck or elsewhere. This will explain why he was treated conservatively with phenobarbital. He did not require as much treatment as had previously been given. He got along quite well and was doing some work with occasional mild attacks until the last illness which brought him into the hospital on March 13, 1951, a little over a year later. He was then brought into the hospital in a series of convulsions, preceded by malaise and fever for one day.

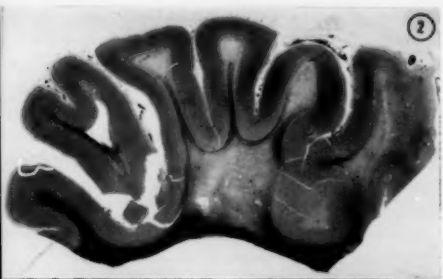
Recovery of consciousness did not occur and we may call the condition status epilepticus. That is an arbitrary definition. Status epilepticus is in fact only an extreme form of periodic grouped seizures and may in fact begin with a series of attacks with recovery of consciousness between attacks. More usually a sudden onset of perhaps 20 attacks the first day is followed by 40 or more the second day and then 60 a day for several days, then a diminishing frequency in similar steps in sequence of 60, 40, 20, 0. It may be seen in the same patient on another occasion as one attack one day, three the next, five the next, three the next, two, then one. In the second occasion consciousness may be retained in the intervals. It is important to recognize that epilepsy which occurs in periodic bursts of attacks may take the form of "status epilepticus." The important feature is increasing frequency to a peak which is followed by a natural decline in frequency until the next episode.

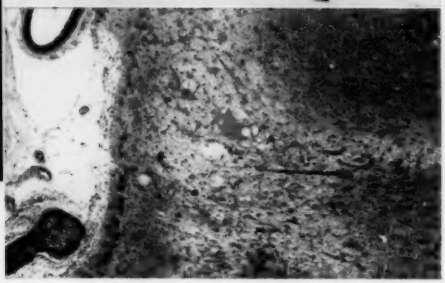
The interval between episodes may be months or years; in some patients there are only one or two in a lifetime. This patient then, I would say, was suffering from status epilepticus. The attacks were generalized whereas they had been focal before, but in status epilepticus generalization is the rule in spite of focal cause. In addition there was fever, which is a regular feature of status epilepticus known since its description by Bourneville. That one pupil was dilated was probably only an indication of asymmetrical exhaustion of the brain. The attacks responded to intravenous medication, and as soon as the attacks began again the physician used a further large dose of intravenous barbiturate. This unfortunately is a common practice. The aim seems to be to suppress the attacks at all costs. Analysis of a number of cases of status epilepticus by Robertson and myself some years ago[3] showed that whatever the intensity of treatment it reaches a peak frequency and then declines. The peak frequency of the episode is delayed by heavy sedation, but status epilepticus has a tremendous momentum and requires very high doses of sedatives to cause even a temporary halt. In the treatment of status epilepticus we should not be afraid of the recurrence of the attacks provided they are not such as to progressively embarrass the patient's circulation and respiration. The epilepsy should be allowed to continue in mild degree until its crisis is passed. To try to keep convulsions entirely suppressed only leads to overdosage of therapy. It appears to me that something of that sort happened here. Shortly after this, his respirations ceased, heart sounds became slow, faint and irregular, and he expired within a short time after admission to the hospital.

We are no doubt expected to implicate a recurrence of Hodgkin's disease in this terminal event. But how could a tumor, after this long interval of freedom, suddenly in the course of a few hours cause all this disturbance, unless by causing a subarachnoid hemorrhage or by causing an acute hydrocephalus. In either case the symptoms would not be these. This picture to me is the onset of status epilepticus in a patient who had already an epileptic tendency. But the epilepsy necessitates a residual scar. How could such a scar arise from a cranial lesion? When I saw this man in 1950 I was impressed by the fact that he had very little hair left on the right side of his head. He had evidently had extremely intense x-ray therapy, directed almost entirely to the right temporal region as judged by the depilation. Therefore I think it likely that the temporal lobe epilepsy and status epilepticus were the result of the intense x-ray therapy and not the Hodgkin's disease. If this was an extracerebral deposit of Hodgkin's disease in the beginning, it would have been situated at the base of the skull, and terminal residual scarring there would be unlikely to be an epileptic focus. Status epilepticus is an illness with extremely high mortality, but I would also feel that 8¾ gr. of intravenous barbiturate must be blamed in part for the final outcome. I would conclude that the condition was status epilepticus from temporal lobe damage following irradiation, complicated by barbiturate intoxication, with a history of Hodgkin's granuloma, probably with extracranial deposits now no longer present.

PATHOLOGIC DISCUSSION

DR. FOLEY: Postmortem examination was restricted to the head. The dura and the venous sinuses were normal. Dr. Raymond Adams cut the brain after it had been fixed in formalin. The only abnormality on the surface of the brain was a small (0.5 cm.) depressed, orange-colored scar in the second temporal convolution of the right hemisphere, near





See text for description of figures.

the junction of the temporal and occipital lobes. There was a small defect in the arachnoid over this scar. The surfaces of the hemispheres were not flattened and there were no temporal or cerebellar herniations. On coronal section, the body of the right caudate nucleus was reduced in bulk and was orange-brown in color. The cortex was destroyed near the scar and the white matter of the adjacent convolutions and the centrum of the right temporal lobe was reduced in bulk and varied from gray to light brown in color (figure 1). The right internal capsule was thin. Both lateral ventricles were slightly dilated, the right more than the left and the right temporal and occipital horns were more dilated than any other part of the ventricular system. Minute foci of brownish discoloration were seen in the left globus pallidus and convolutional white matter of the left inferior parietal lobule.

On microscopic examination, the scar seen on the surface and on section consisted of complete replacement of the gyrus by dense gliosis and fibrosis. The rest of the temporal region seen to be affected in the gross showed no change in general architectural pattern. The most striking change was an almost complete loss of myelin sheaths and nerve fibers of the convolutional white matter, with diffuse gliosis (figure 2). Some nerve cells were lost in the cortex overlying these areas, especially in the deeper layers, and there was some replacement gliosis and liquefaction (figure 3). There was a diffuse but incomplete loss of nerve fibers with gliosis in the white matter of the centrum of the temporal lobe and in the internal capsule.

Small foci of necrosis with hemosiderin in the walls of nearby vessels were seen in the globus pallidus. The smaller nerve cells of the caudate were not present,

and only a few large nerve cells remained. Replacement gliosis was intense. Hemosiderin in phagocytes was present around many of the blood vessels. The putamen was unaffected.

Mineralized nerve cells were found both in the caudate and at the edges of the zone of necrosis in the temporal cortex.

There were no significant changes in any of the blood vessels.

No evidence of tumor was found in any of the sections of brain or meninges.

The pathologic findings in this case are consistent with the diagnosis of radiation necrosis of the brain. It is remotely possible that the area of complete focal necrosis in the second temporal convolution was the site of radiosensitive tumor, but the incomplete affection of such a widespread area of brain without loss of architectural pattern makes it most unlikely that the entire area or any part of it was involved by tumor. In the light of the pathologic data, it seems more likely that the original intracranial disorder was due to a radiosensitive lymphomatous tumor of the meninges. A delayed radiation necrosis of the right hemisphere, with maximum involvement of the temporal lobe and formation of meningocerebral scarring resulted in seizures. Under this interpretation, the additional radiation given for the seizures was ill-advised and probably increased the original extent and degree of damage in the right hemisphere. Death was due to the seizures and their complications.

In reconstructing this case, we might consider briefly certain facts about the behavior of lymphoma in the brain and its coverings. Hodgkin's paragranuloma does not involve the brain, the meninges or the skull. Hodgkin's granuloma may involve the meninges but does not metastasize to brain substance. Hodgkin's sarcoma may involve brain substance. Yet of all the types the sarcoma is the least radiosensitive, and for this reason it is unlikely that there was a tumor in brain substance in the present case. One must, therefore, return to the probability of a meningeal Hodgkin's granuloma destroyed by radiation, but with resulting damage to brain substance by the radiation.

This case has many resemblances to those described by Pennybacker and Russell,[4] who reported nine cases "in which harmful effects to the brain have followed standard dosages and technique without serious superficial damage, and at long intervals after the termination of treatment. . . . In brief, the lesion was an extensive subcortical necrosis, maximal in the field which received the most radiation. In some cases the clinical effects came on after a long latent interval with the suddenness of a vascular accident; in others they were slowly progressive, clinically suggesting a recurrence of the tumor for which the radiation treatment had been given."

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CASE REPORT

Nonchromaffin Paraganglioma of Middle Ear and Abdomen

J. L. Garvey, M.D. and
D. B. Claudon, M.D.

NONCHROMAFFIN paragangliomas of the middle ear are peculiar neoplasms that have been reported with increasing frequency since Rosenwasser[1] first recognized and described a typical case in 1945. In commenting on the clinical histories of 18 cases reported to January 1951, Dockerty, Love and Patton[2] pointed out that long periods of deafness, tinnitus, otitis media, mastoiditis, and palsy of various cranial nerves were the symptoms most commonly encountered. Multiple nonchromaffin tumors have been reported by Kipkie,[3] Cragg,[4] Lattes and Waltner,[5] and others. Winship, Klopp and Jenkins,[6] and Smetana and Scott[7] have described malignant cases but LeCompte[8] was impressed by the extreme rarity of metastasis and felt that definite and satisfactory evidence of malignancy is seldom available. As knowledge has increased, cases previously called "granular-cell myoblastoma" or "angioma of the middle ear have been reclassified as nonchromaffin gangliomas.[9,10] Since this neoplasm is still so little understood, the description of another variant seems justifiable.

REPORT OF CASE

A 20 year old man employed as a newspaper compositor was admitted to the neurology service at Columbia Hospital on May 27, 1950, complaining of headaches and blurring of vision in the left eye.

He had been in good health until October 1949, when there was onset of weakness of the right side of his face within a period of several weeks. Bowling or other exercise resulted in transient headaches. In April 1950, the patient complained of blurred vision in the left eye and noted increasing difficulty in writing. He had lost approximately ten pounds since January.

Past medical history revealed that in 1947 the patient had been unconscious three minutes following a head injury while playing football. He had subsequently become completely deaf in the right ear, but felt that the injury had merely aggravated a preexisting impairment of hearing which had been present since the age of 15 years. Social and family history were non-contributory.

Physical examination upon admission revealed total deafness in the right ear and a complete peripheral paralysis of the right facial nerve. The uvula deviated to the right on phonation. There was slight bilateral horizontal nystagmus, diminution in the corneal reflex, and "early" papilledema of the optic discs. The patient exhibited slight instability in balance.

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Examination of the ears by an otologist showed a normal left tympanic membrane. All landmarks were missing on the right. The right tympanum bulged and was bright red. When it was incised, profuse bleeding occurred and was controlled with difficulty by packing the external auditory canal. A tentative diagnosis of aneurysm of the right middle ear was made by the examiner.

Roentgenograms of the skull with particular reference to the right temporal bone indicated destruction of the apex of the petrous pyramid between the carotid canal and the jugular fossa. The internal auditory canal was dilated (figures 1 and 2). Diagnoses of acoustic neuroma or hemangio-endothelioma were suggested by the radiologist.

Exploratory craniotomy was performed on June 2, 1950, through a right temporo-occipital incision. A pulsating lesion "about the size and color of a large Concord grape" was found extending from the middle ear into the right cerebellopontine angle. The mass was thought to be an aneurysm and therefore was not biopsied.

Immediately after operation the patient's condition was satisfactory, but pronounced nystagmus to the right, diplopia and persistent right facial paralysis were observed. Onset of nausea on the second postoperative day was followed by sudden collapse. An arteriogram obtained at this time revealed an exceedingly vascular lesion of the right middle ear. The patient's condition rapidly grew worse. He lapsed into coma and died suddenly on June 5, 1950. Lumbar puncture performed shortly before his death revealed an initial cerebrospinal fluid pressure of 500 mm. of water. The fluid at first was xanthochromic, then bloody.

Pertinent findings at autopsy were in the skull and abdomen. A fleshy, granular, beefy-red, friable, extremely vascular, 2.8x 3 x 3.5 cm. tumor replaced the medial half of the right petrous pyramid. The superior and posterior walls of the pyramid were paper-thin or missing entirely; the anterior and lateral surfaces were not appreciably altered. Further investigation established that only the right facial and auditory nerves were incorporated within the tumor; the remaining cranial nerves were intact. The bulk of the neoplasm was in the vicinity of the inner ear and jugular bulb. The right internal carotid artery coursed through the tumor but was not appreciably altered from normal. The venous sinuses of the posterior fossa were normal (figure 3).

A spheroidal, 250 gram, 3.5 x 5 x 6 cm., yellowish-gray, encapsulated mass was found in the abdomen lying in the retroperitoneal tissues on the right side of the vertebral column immediately below the renal pedicle. The tumor was attached to the right lumbar sympathetic chain between the first and third ganglions. On section the cut surface bulged unevenly above a thin capsule and was composed of many small, greyish-yellow islands of rather granular tissue surrounded by an irregular fibrous network. The abdominal tumor was firmer and much less vascular than the skull lesion. The cut surface superficially resembled that of a leiomyoma (figure 4). There were no adhesions to the capsule or evidence of pressure on adjacent structures. Search of the adrenal areas and along the aorta did not reveal other tumors.

Microscopic examination of routine hematoxylin-and-eosin-stained sections revealed a basic similarity between the tumors of the middle ear and abdomen. The former was more vascular and had invaded and destroyed the middle ear and petrous pyramid. The latter was less vascular and showed no evidence of spread beyond its capsule. Both were composed of clumps or sheets of medium-sized cells with abundant eosinophilic cytoplasm and small, round or oval nuclei containing vesicular chromatin. Nuclei were usually eccentrically placed and showed little pleomorphism. Mitoses were rare. Cell boundaries were indistinct. Considerable fibrosis and a sprinkling of lymphocytes and plasma cells accompanied the growth of the middle ear lesion; sections from bony areas revealed atrophy and pressure necrosis of both cancellous and cortical bone. There was no fibrosis or leukocytic infiltration in the abdominal lesion, but many areas of edema and beginning ischemic necrosis were seen.

Connective tissue and elastic tissue stains revealed essentially the same features as the routine stains. Wilder's silver impregnation method brought out a delicate network of reticulum which surrounded capillaries and small nests of tumor cells. Results with Gomori's chromaffin stain were not uniform; occasional tumor cells contained purple or violet cytoplasmic granules although a large majority did not. No appreciable difference was noted between the two neoplasms in this regard.

Pieces of fresh tissue from each specimen did not turn green when immersed for five minutes in 5 per cent ferric chloride solution

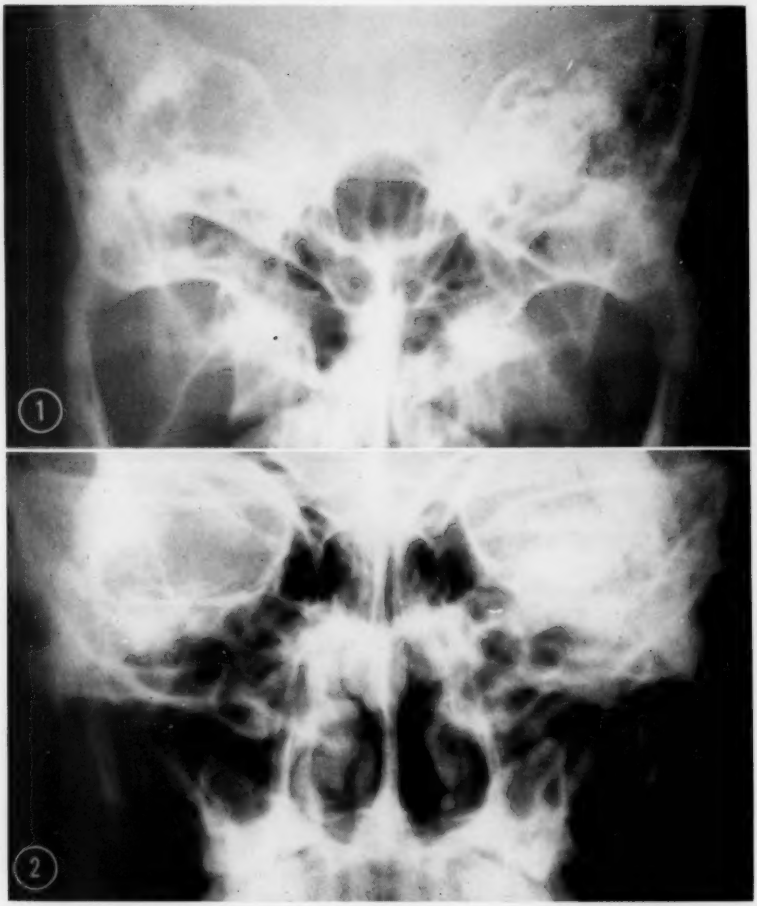

FIG. 1. Erosion of the medial portion of the right petrous bone with preservation of the petrosal ridge. Mastoid cells on right not as clear as on left.
FIG. 2. Another view illustrating the considerable degree of destruction of the apex of the right petrous bone.

(Vulpian reaction),[4,11] nor did frozen sections of fresh tissue exhibit chromaffinity after being mounted on slides in 2.5 per cent potassium dichromate solution.

DISCUSSION

It is now generally accepted that the glomus jugularis, carotid body, aortic bodies, and other less-constantly located structures are components of the nonchromaffin paraganglionic system. This system differs physiologically, endocrinologically, and histologically from the chromaffin or sympathetic system. The paraganglia are probably a series of spe-

FIG. 3. Appearance of the tumor in the right petrous pyramid at autopsy.

FIG. 4. Cut surface of the abdominal tumor.

cialized neuro-epithelial cells[12,13] acting as chemoreceptors sensitive to changes in oxygen tension, pH, temperature of the blood and other stimuli.[14–17] They do not elaborate epinephrine,[4,18] lack affinity for chrome salts,[11,13] and are innervated by sensory fibers from the craniosacral division of the autonomic system.[19,20]

The two neoplasms in our patient probably arose independently, but at approximately the same time. In view of the history of impaired hearing since the age of 15, it is possible that growth extended over a period of five or six years.

There was no historical or clinical evidence of endocrinologic activity of the tumors. Although the patient was near the end of puberty, development of secondary sexual characteristics and rate of growth were normal.

There was no history or clinical evi-

dence of hypertension. The patient's blood pressure and pulse were stable within normal limits on numerous examinations subsequent to the injury in 1947.

It is interesting to note in this case, as in several others,[2,8,21] that few of the classical symptoms appeared before the middle ear neoplasm had attained considerable size and had produced serious damage to the middle ear and surrounding structures. There was no clinical evidence of the abdominal tumor at any time.

Experience with this patient indicates that a high index of suspicion is necessary with patients who complain of sudden onset of unilateral hearing impairment, tinnitus, otitis media, or palsy of the seventh or eighth cranial nerves. Careful x-ray examination of the petrous portion of the temporal bone frequently offers a means of early diagnosis. Carotid arteriography was used successfully by Alexander, Beamer, and Williams[21] to determine the operability of their patient's tumor, but in many cases the procedure has not been helpful.

Surgical removal of nonchromaffin paragangliomas of the middle ear is very difficult when this growth has destroyed the petrous bone or perforated the tympanic membrane. The operative mortality is high because of the extreme vascularity and inaccessibility of most of these lesions.[2,19] Irradiation therapy has produced favorable results in occasional cases[21,22] and perhaps is worthy of consideration.

SUMMARY

1. A case of nonchromaffin paraganglioma of the middle ear and retroperitoneal area of the abdomen has been reported.

2. Clinical symptoms began with unilateral impairment of hearing in 1935. Complete deafness followed an injury to the affected ear in 1947. Since acute symptoms did not appear until seven months before the patient's death in June 1950, a causal relationship between the injury and development of the neoplasm is doubtful.

3. The importance of early diagnosis and the difficulty of differential diagnosis later in the course of the disease is emphasized by this case.

4. An attempt at surgical removal of the middle ear tumor was unsuccessful.

The authors wish to thank H. P. Maxwell, M.D., T. L. Tolan, M.D. and S. A. Morton, M.D., who saw the patient in consultation.

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After the tonic spasm has lasted for a few seconds or for one, two, or three minutes, the stage of clonic spasm comes on. Its onset is not sudden but gradual. In the most typical cases the tonic spasm becomes distinctly vibratory in character; the vibrations become less frequent and more distinct, until they consist of a series of clonic contractions. The remissions, as they become longer, become greater in degree, until at last they become complete intermissions, and towards the end of the fit the limbs are completely relaxed between the successive shock-like jerks. As the remissions become greater the contractions apparently become stronger, but the increase in strength is apparent only, and due to the fact that each contraction starts from a greater degree of relaxation. The spasm ends by the remissions becoming longer and longer until, when they amount to one or two seconds, the jerks cease; but the last contraction is often as strong as any which have preceded it.

The muscles involved in the clonic spasm are usually the same as those which were involved in the tonic spasm. As the clonic stage develops, the limbs retain the same position in which they were fixed by the tonic spasm, commonly with the arms in flexion and the legs in extension. During the intermissions the limbs may fall from the position they occupied before, but each clonic jerk tends to bring them back to it. In the most frequent posture, for instance, in each jerk the elbows are flexed, and the wrists flexed still more strongly, and the fingers jerked at the metacarpo-phalangeal joints.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Neurology

The Extrapyramidal System

An Inquiry into the Validity of the Concept

Russell Meyers, M.D.

If one were to ask the well informed neurologist to itemize the extrapyramidal diseases he would in all likelihood receive the following reply:

Chorea	Athetosis
Parkinsonism	Dystonia musculorum
Myoclonus	Ballism
Tic twitchings	Myorhythmia
Wilson's disease	Westphal-Strümpell's disease
Spasmodic torticollis	Huntington's chorea
Jakob Creuzfeldt's disease	Hallervorden-Spatz' disease
Pelizaeus-Merzbacher's disease	Mount-Reback's disease

Were one then to ask for a synopsis of the clinical manifestations of these diseases, particularly for those signs and symptoms by which they may be distinguished from other nervous disorders, the answer would very likely be cast in the following terms:

Hyperkinesia (patterned; non-patterned)
Akinesia-hypokinesia (poverty of movement; defect in automatic associated acts)
Alterations in myotonus (rigidity; hypotonia)
Recession of symptoms during sleep and augmentation during emotional action

The neurologic informant would probably add that the extrapyramidal disorders do not result from any single etiologic agent, nor yet from any single

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Presented at the Research Seminar, State of Illinois Medical Research Institute, Galesburg, November 19, 1952.

pathologic process, but that, on the contrary, they may be produced by multifarious etiologic agents and cerebral pathologic processes, such as

Infectious agents (bacterial, viral, parasitic)
Vascular disorders (thrombotic, embolic, hemorrhagic)
Neoplastic processes (primary, secondary)
Metabolic disorders (O_2, CH_2O, Cu, amino acids, kernicterus, etc.)
Physical agents (heat, trauma)
Drugs, toxins (gaseous, metallic poisons, etc.)
Degenerative and dysplastic processes
Heredity(?)

Let us suppose our inquirer now seeks information on precisely what is meant by the generic term, "extrapyramidal diseases." The rejoinder will probably be simple and sublime: the diseases of the extrapyramidal system. And if he pursues the inquiry to the next reasonable question, asking what precisely is meant by the extrapyramidal system, he will likely be enlightened by the statement that the system embraces "all efferent mechanisms apart from the pyramidal tract which have to do with motor activity." [14,37,53,56,79,108]

Thus far, things have gone very smoothly. To all outward appearances the correspondents have been in harmonious communication with one another, and their verbal exchanges, cast in proper linguistic and syntactic forms, have brought about the desired results. All questions posed have been answered; the communicative episode has come to an end; and each correspondent, exhilarated by the experience, goes happily on his way ready to encounter fresh problems. Where at the outset there was but one, there are now two well-informed beings capable of spreading the word.

Unfortunately, such an enviable state of euphoria is not likely to invest the serious student in this area, at least, not for some time to come. To say that he is sorely perplexed by the existing state of affairs is to put the matter in the most euphemistic terms possible. Everywhere he encounters irreconcilable pieces of data, many of which appear to be frankly contradictory and mutually exclusive. And when he attempts to bridge the factual difficulties by formulating hypotheses and other interpretative accounts, particularly in the endeavor to fashion rational therapeutic approaches to the clinical problems posed by those suffering from the extrapyramidal diseases,[2,15,18,19,20,25,41,64,112,115,117,119,121,125,128,129,130,138,159] his confusion becomes even more apparent.

METHODOLOGIC APPROACH

Confronted with such perplexities, the investigator finds it natural to assume that they inhere within the complexity of the objects of study themselves. In such circumstances he accepts his unhappy lot with graceful resignation and commendable determination and continues the dogged scientific fight along the old lines, looking hopefully toward eventual conquest of a stubborn foe. But in theory, at least, there is another possibility that the difficulties rest not so much with the objects of study themselves (though these may be formidable enough) as with the formulations and unvoiced

assumptions the investigator employs in dealing with them. Such an alternative may not be as preposterous as seems on first encounter.

Let us view the matter as it might appear to the non-medically-trained student of general semantics.[60,78,87,123,124,132] The answers furnished above by our neurologic informant constitute formulations, i. e., maps which he habitually presses into service whenever he deals with the organismic events pertinent to the extrapyramidal system and its diseases. Such organismic events, taken together, constitute the "referents" or "territory" about which he talks and writes and to which he, as basic scientist and/or clinician, actually endeavors to adapt. It is now apparent that the investigator can effectively find his way about an area of research and so achieve desired ends only if the map he employs corresponds closely to the territory he encounters. Conversely when, though faithfully following it, he finds himself again and again frustrated, he is obliged to question the validity of the map. (He would be a naive traveller indeed who insisted that, regardless of the frequency with which his map leads him to impasses, it is to be retained and cherished as more "real" than the territory itself.)

In this presentation the writer proposes to examine the current neurologic maps bearing on the extrapyramidal system with a view to ascertaining how closely they represent the territory. Initially, the reader's attention is invited to certain crucial terms appearing in current definitions of the extrapyramidal system. These are: "all efferent mechanisms....", "....apart from the pyramidal tract....", "....having to do with...." and "....motor activity." We shall address ourselves in part to an analysis of these terms and phrases, and in part to their synthesis in what purports to be a scientifically meaningful statement. If we find any or all of them wanting in precision, more especially if we find them lacking in identifiable counterparts in the world of organismic neurologic experience, we shall be obliged to question the validity of the conventional maps of the extrapyramidal system and its diseases and perhaps, in the end, to revise or reject them in favor of other more promising formulations.

For psychologic reasons, the critical examination of one's long-employed maps is not an easy task. Formulations once accepted and used, whether scientific, religious, philosophic or esthetic, exhibit a strong propensity to become personal, even group, national and cultural prejudices. And despite the obligations imposed upon scientists by scientific method,[113,114] few of us routinely examine them in an impersonal, critical way. When we do turn to them we are often driven by necessity rather than choice. A brief illustration will point this up.

Few, if any, physicists of the first decade of the current century were even vaguely aware that their endorsements of euclidean geometry and newtonian formulations concerning matter, energy, space and time constituted prejudices possessing a fair degree of internal consistency rather than eternal verities. There was, however, one individual who viewed matters otherwise, namely, Albert Einstein. Perplexed by the ineptitude of the orthodox mechanistic doctrine of his day for reconciling electromagnetic phenomena with

the disclosures of Michelson and Morley on the invariability of the speed of light, this investigator arrived at a realization of the strictly axiomatic character of euclidean and newtonian formulations. This in itself was a bold, even a heretical, step. But in taking it, Einstein achieved a freedom from the time-revered linguistic habits which held his fellow physicists captive. By 1905 he had made use of an already constructed "imaginary" geometry (that of Riemann), based on non-euclidean axioms, to fashion a non-newtonian (more accurately, a meta-newtonian) "map" of the physical universe. This (in turn) was rapidly improved and extended and is now known as the general theory of relativity. For the most part, Einstein's contemporaries had to be driven to the task of reexamining the premises of the older concepts. To their great credit, however, they did examine them, did recognize their prejudicial nature, and did adopt the new axiomatic outlook, incidental to which the way was paved for the atomic age. What is of equal importance is the fact that physicists and their fellow investigators in closely related disciplines are now keenly aware that the current relativistic maps do not in themselves constitute eternal truths but merely tentatively useful formulations. As never before in the history of science they are resolved that these shall not become the pet prejudices of a new generation.[46]

There is a deep moral in this for those seriously engaged in the task to which we now address ourselves. The extrapyramidal system and, for that matter, the pyramidal system are not demonstrated facts, as many students of neurology appear to believe, but man-made concepts, i. e., verbal maps, intended to describe and account for certain empirically observable aspects of the structure and function of the nervous system. There is nothing sacred or inevitable about them; they are not and never can be more valid than the organismic events they are intended to represent.

DEVELOPMENT OF THE EXTRAPYRAMIDAL CONCEPT

The current contention is that the extrapyramidal system possesses anatomic and physiologic characteristics of its own and that, when certain of its parts are damaged by disease or experimental design, clinical signs and symptoms in the form of extrapyramidal disorders and disease entities supervene. A brief historical digression may serve to demonstrate how, at various crucial turns in the development of the concept, inference was mistaken for fact and errors of logic were compounded.

Prior to 1800, no attempt was made to fractionate the brain into anatomic parts mediating special functions. The first serious effort along this line was made in 1803 by Franz Gall,[54] a Viennese practitioner with a remarkable talent for descriptive and comparative neuroanatomy. Gall endeavored to interpret personality in neurologic terms and, with the later aid of Spurzheim, became the author of phrenology. In evolving phrenologic doctrine he inadvertently fell into two errors. First, unaware that "the word is not the thing," [87] he adopted the prevailing faculty-psychology of his day and equated terms like "acquisitiveness," "amativeness," "self-esteem" and "philoprogenitiveness" with brain "functions," the anatomic *loci* of which only awaited discovery; and second, he repeatedly committed the logical fallacies of *petitio principii, post hoc ergo propter hoc* and *argumentum ad hominem.* These ultimately proved fatal to phrenology as a science, but the underlying notion concerning the localization of cerebral functions persisted, profoundly

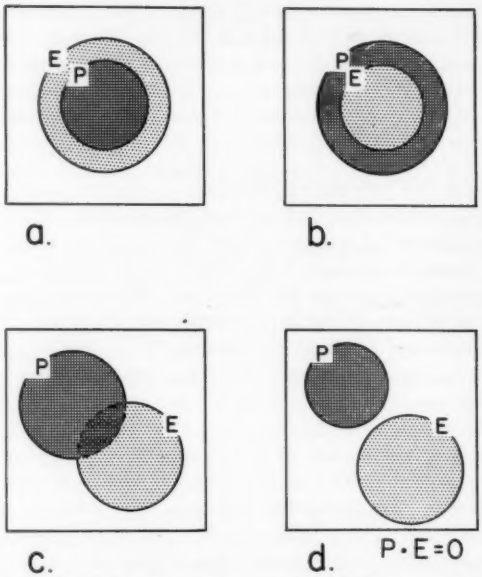


FIG. 1. Schematic representations of four (among several) possible relationships between the "pyramidal" (P) and "extrapyramidal" (E) systems, arranged as prescribed in modern symbolic logic. The relationship depicted in *d* corresponds to most current-day definitions of the extrapyramidal system and has been conveniently expressed in the form of a Boolean algebraic equation: $P \cdot E = 0$. See text for discussion.

influencing Gall's contemporaries and many of those who followed. Credit for obtaining the first supportable evidence of cerebral localization goes to the French pathologist, Bouillaud,[11] who identified the frontal lobes as the seat of speech in 1825. A refinement of this formulation was soon achieved by Marc Dax[33] and later by Paul Broca.[13] Within another decade the spectacular disclosures of Fritsch and Hitzig[47] concerning the excitable motor cortex emerged from the Franco-Prussian war and provided welcome support for Jackson's[73] clinical inferences concerning the motor makeup of the cerebral cortex. There now ensued an era of feverish neurologic research, astute observations and ingenious speculation, and by the time another half century had passed the currently popular mosaic ideas of brain localization had been largely fashioned. It was in this setting that the concept of an extrapyramidal system came into being. Additional details of the story will be elaborated in later paragraphs.

At this point, profitable discussion of our subject requires clear recognition of the historical circumstance that the concept of the exrapyramidal system was antedated by and throughout the years since its inception has been conditioned upon the concept of the pyramidal system. For this reason the validity of the former depends in considerable measure upon how convincing

a case can be made for the latter. (This much follows from the contention that the extrapyramidal system consists of "all efferent mechanisms *apart from the pyramidal tract* which have to do with motor activity"). As a neurologic map, the definition clearly depicts the circumstance of a dichotomy, in view of which the question arises as to whether a phenomenal dichotomy is discoverable in the territory itself.

"... APART FROM THE PYRAMIDAL TRACT ..."

For a sharper delineation and readier manipulation of this question we may recast the pyramidal-extrapyramidal dichotomy in terms acceptable to the student of modern symbolic logic. Here we find available a highly useful tool, Boolean algebra, which for some years has been advantageously employed in the resolution of both pragmatic and theoretic problems in the scientific, sociologic and humanitarian realms.[98]

In figure 1, the squares represent the framework within which the discussion must by agreement be confined – for example, the neuromuscular activities of the organism as distinguished from, say, astrophysical, esthetic, or ethical considerations or any of a host of other subjects that might conceivably engage attention. The circles, P and E, within the squares stand for the "pyramidal" and "extrapyramidal" systems, respectively, and their topographic arrangements express theoretically possible relationships between P and E. Four instances (only) pertinent to our inquiry have been depicted. In *a*, E includes P (as the United States may be said to include Ohio); in *b*, P includes E; in *c*, P and E are partially but inseparably overlapped, in the sense that they share structures and/or functions; and in *d*, P and E are dichotomized.

Now, if the conventional definition of the extrapyramidal system warrants the faith so generally reposed in its validity, it should be possible by appeal to facts, that is, to phenomenal relationships demonstrable by operational procedures,[12] to show that the circumstances depicted in *d*, and not those in *a*, *b*, and *c*, are met. The Boolean algebraic equation which briefly expresses these circumstances is $P \cdot E = 0$, which means that the product* of P and E is zero. It signifies that there is no sharing or overlapping in an anatomic or physiologic sense. This does not, of course, preclude their harmonious collaboration in the over-all interests of organismic economy. Applied to a community of humans, the same formula would epitomize the relations of, say, the fire department to the education department; each has its own structure and function, separate from the others.

Our question now becomes: "How closely do the observable data concerning the pyramidal-extrapyramidal dichotomy fit the conditions of the Boolean equation, $P \cdot E = 0$?"

*In Boolean algebra the term "product" conveys a quite different meaning from that denoted in standard algebra. It expresses the presence, absence or degree of overlap of common features. In the present case, the formula accords with generally accepted definitions in asserting to the absence of overlap.

A. THE PYRAMIDAL SYSTEM. As gross landmarks, the medullary pyramids (from which the pyramidal tract and pyramidal system derive their names) were well known to the older anatomists. But the fact that they give transit to the extensive neuronal fibers now known to course through them was not appreciated until the latter half of the nineteenth century when, in consequence of energetic studies by Türck, Flechsig, Fritsch and Hitzig, Ferrier, Jackson, Horsley, Kölliker, Munk, Goltz and others, the idea of a pyramidal tract emerged. The pertinent observations were in no small measure made possible by a number of fortunate circumstances: (a) the conspicuous anatomic character of the pyramids; (b) the presence of grossly traceable white fascicles (the corona radiata) converging upon the internal capsule and pes pedunculi and coursing through the midbrain crura and pyramids to decussate at the lower end of the bulb; (c) the existence in this pathway of long, densely medullated fibers, readily susceptible of demonstration by the myelin sheath stains then available; (d) the anatomic accessibility of the better portion of the sensorimotor cortex on the hemispheral convexities; and (e) the clinical frequency of apoplectiform hemorrhage in the internal capsule.

The studies alluded to above provided important, though still decidedly incomplete, data bearing on the pyramidal tract. When, a few years later, neural counterparts of the cord-destined pyramidal paths (the medial and lateral corticobulbar tracts) were recognized as playing upon the motor nuclei of the brain stem,[34,35] the concept of the pyramidal system emerged full-fledged. Thus envisioned, the system was essentially an anatomic construct. However, it was early endowed with physiologic connotations and so remains to the present day.[88] We must now inquire to what extent its anatomic and physiologic characteristics may be considered to stand "....apart from...." the "extrapyramidal system" and vice versa.

(a) *Anatomic Considerations*: The pyramidal tract was at first loosely equated with all corticospinal fibers, without regard to their sites of origin, much less to the possibility of multifarious functions. It gradually became evident, however, that in all parts of its course the tract is interspersed with a considerable number of descending axones (amounting in some estimates to between 30 and 50 per cent) whose origins are completely unknown.[57,89,91,92,93,95,144] In an attempt to circumvent growing difficulties of this sort, the pyramidal tract was conceived of as being equated with the axones of Betz cells descending from the fifth layer of the pararolandic cortex to the spinal cord.[66] But for the following reasons this revision proved even less tenable than the first.

1. If the ratio of cells and fibers is given due consideration, it appears that less than 5 per cent of the Betz cells of the motor cortex contribute fibers to the corticospinal tract.[108,152]
2. By actual count, Betz cell axons constitute less than 3 per cent of the fibers which, in the gross aggregate, make up the primate pyramidal tract.[89,91,92,93,144,152]

3. The collaterals of many Betz cell and other area 4 fibers apparently terminate upon cells other than those of spinal and bulbar anterior horn cells and their internuncial neurons, for example, upon pontine, nigral, reticular, pallidal, and striatal nuclei.[3,14,65,94,108,147,148] Furthermore, currently available data do not permit exclusion of the possibility that Betz cell axones terminate at pontine, striatal, reticular and other waystations alone. This being so, the categorical identification of Betz cell axones as pure pyramidal elements seems hardly justifiable.
4. After removal of the cortex of area 6, degenerating fibers which run with the pyramidal tract through the brain stem and into the spinal cord have been regularly demonstrated in the monkey.[82]

From these data it is apparent that the anatomic make-up of the pyramidal tract and, by the same token, the pyramidal system, is to a considerable extent shrouded in uncertainty, a fact upon which Sarah Tower[144] has commented in another connection.

(b) *Physiologic Considerations*: Historically, two broad functions have been imputed to the pyramidal tract: (1) the mediation of voluntary (volitional, willed) movements; and (2) the mediation of fine, discrete, phasic movements. These we shall consider separately.

(1) *Voluntary movements*: Shortly after the discovery of the motor excitable cortex by Fritsch and Hitzig[47] the gyri adjacent to the rolandic fissure were looked upon as the center of willed movements.[28,43,61,88] And since the pyramidal tract had been traced from this center to the brain stem and cord, it seemed unassailably logical to early investigators to assert that the transmission of volitional impulses is the unique business of the tract. (It is of considerable interest that a volitional function has never been seriously proposed for any other corticofugal pathway). With few modifications this idea prevails today.[14]

Unfortunately, two disconcerting circumstances interfere with acceptance of these popular notions. The first relates to the terms themselves, "voluntary," "volitional" and "willed," and their linguistic antitheses, "involuntary," "non-volitional" and "unwilled." That these are used at all in scientific discourse would seem to imply that recognizable differences exist between two distinct classes of organismic activity and that whenever occasion demands they can be reduced to criteria by means of which the one may be unmistakably marked off from the other. (If such is not implied, the propriety of using the terms in scientific discourse becomes nil and the popular concept of the role of the pyramidal tract in transmitting voluntary impulses becomes a mere fiction.)

But when the literature germane to the subject is examined in the light of modern operational principles, one stubborn fact becomes evident: that criteria have not thus far been formulated by means of which voluntary activity can be dependably differentiated from involuntary. Such distinctions as now obtain appear to be rooted in stoichiologic intuition and perpetuated

by linguistic habits of dubious origin. From the philosopher's viewpoint, they fail to satisfy the requirements of both metaphysical determinism and indeterminism, for under the former, free will becomes a mere illusion, phenomenologically dependent upon the observer's ignorance of the compelling antecedent determinants; and under the latter, it becomes a special manifestation of the chaos and chance that probabilistic quantum theory envisions,[39] hence quite unlike the directive and purposive phenomenon its earnest advocates consider it to be.

This brings us to our second consideration. From the viewpoint of the psychologist and physiologist, distinctions in kind between voluntary and involuntary are equally unsatisfactory. The researches of Hudgins,[67] Menzies,[107] and others[27,99] who have successfully conditioned involuntary effectors (for example, the musculature of the iris and the unstriated muscles of the peripheral vascular tree) to subvocal cues and thus brought them under intrapersonal symbolic control [the will?] have tended to undermine rather than underscore the imaginary line generally presumed to separate voluntary from involuntary behavior.

Whatever is loosely referred to by the term voluntary behavior, it is certainly not completely and enduringly abolished by section of the pyramidal tracts as the latter course through the midbrain peduncles and swing into the upper cervical cord.[14,21,22,42,88,97,143,150] In laboratory animals, voluntary movement is severely impaired by such interruption but is not enduringly abolished. The human, in whom will is asserted to be more highly developed and readily demonstrable than in any other animal, constitutes no exception.[41,117,118,125,128,151]

But if all we can say is that damage to the pyramidal tract seriously impairs but does not abolish voluntary impulses, we have not demonstrated a distinctive functional role of the pyramidal system, for damage to many other parts of the nervous system, such as the corpus restiforme, the uncinate bundle of Russell, the decussation of the brachium conjunctivum, the rubrothalamic fibers of Forel's H_1 field, the ventrolateral and ventroposterolateral thalamic nuclei and the premotor cortex, has a comparable effect.

In short, no operational experiment, physiologic or psychologic, has yet been devised by which questions concerning the ancient "volitional-involitional" dichotomy can be satisfactorily settled. And until one is implemented, this criterion cannot be relied upon to distinguish the pyramidal from the extrapyramidal system. Similar remarks hold for the role of consciousness as a factor in voluntary movements.[42,116,156]

(2) We may now examine the second function historically imputed to the pyramidal tract, namely, that of mediating fine, discrete, phasic movements.[14] In this we deal with *praxis* in its most eupractic sense.

Nosologically, the pyramidal tract is at present acknowledged to consist of corticofugal fibers derived from the pararolandic cortex, Brodmann's areas

6, 4, 3, 1, 2 and also areas 5 and 7.* [40,56,95,109,120,157,166] Despite this, many writers adhere to the easily teachable notion that the axones arising from area 4 are somehow the essential elements of the pyramidal tract, in view of which area 4 constitutes the cortical portion of the pyramidal system,[14,48,53] distinguished in this respect from other portions of the excitable motor cortex, for example, Brodmann's area 6, which they designate "the extrapyramidal cortex." Damage to area 4 quite clearly results in a degree of dyspraxia and, if extensive enough, in permanent apraxia or dyspraxia.[48,49,50,53,83,148] From such observations, the concept of the role of the normal pyramidal system in mediating fine, discrete phasic movements was first derived.

But such evidence can hardly be taken as cogent, for while a lesion thus placed certainly damages corticofugal contributions to the pyramids, it also damages many other neural elements arising in the same cortical areas. Some of the latter are said to connect with subcortical nuclei (globus pallidus, N. ruber, S. nigra, C. Luysi, tegmental reticular formation, and so on) and therefore should, on the conventional view, be classified as extrapyramidal. Others, being by definition "non-efferent mechanisms" (e. g., those giving rise to U-fibers), clearly fall outside both the pyramidal and extrapyramidal classes. But to exclude all such non-pyramidal components as playing a role in eupraxia appears to the disinterested observer an exercise of arbitrariness quite beyond warrant.

Furthermore, ample clinical and experimental evidence is at hand [6,51,74,84] to indicate that extensive damage to the premotor cortex (Brodmann's area 6), generally regarded as an integral part of the extrapyramidal system,[17,53] also results in dyspraxia. Hence, it cannot properly be asserted that the mediation of eupraxia is the unique business of the pyramidal system. The fact is that it has not been possible at cortical, brain stem or cord levels to ascertain the functional role of the fibers of the pyramidal system for the reason that it has never been possible to examine them independent of numerous concomitants.

Once again, then, the criteria we seek in the pyramidal system have failed to materialize, i. e., the operational requirements of our Boolean equation remain unrealized. One observation emerges with pristine clarity: that the drawing of conclusions concerning the functions of the pyramidal system from data obtained through stimulating, damaging and recording electrical potentials from the anatomic pyramidal tract and/or area 4 [50,52,103] is a dubious procedure. Despite similarity of labels, the pyramidal tract and pyramidal cortex, area 4, cannot be equated with the pyramidal system – even with that part caudal to the decussation of the pyramids.

*As previously observed, this is in no sense an all-inclusive formulation. In all parts of its course, including that through the medullary pyramids, where axones from the pararolandic cortex are least contaminated, the pyramidal tract is abundantly interspersed with fibers of unknown origin (see above).

B. THE EXTRAPYRAMIDAL SYSTEM. We now turn to the extrapyramidal system in the hope that a more satisfactory resolution of our difficulties may be accomplished. Physiologic evidence suggesting that motor activity can be altered by stimulating parts of the nervous system not incorporated within the pyramidal system began to accumulate during the second decade of the current century. For example, Graham Brown,[16] studying an ape in Sherrington's laboratory, reported in 1913 that a postural flexion of the upper extremity maintained by electrical stimulation of the midbrain tegmentum could be promptly changed into a strong phasic flexion by stimulating the midbrain crus in which pyramidal fibers were known to be running. This observation was interpreted to mean that a prevailing posture, induced by stimulation of a non-pyramidal structure (the tegmentum), can be wiped out by stimulation of the pyramidal system.[162,163,164] The idea of a dichotomy clearly inhered within this interpretation.

(a) *Anatomic Considerations*: There is as yet no general assent among neuroanatomists as to just which structures and nerve pathways should be included with and excluded from the extrapyramidal system. Early, the term referred chiefly to the basal ganglia, that is, the neo- and paleostriatum, with or without the thalamus.[96] Somewhat later, extensive connections between widely distributed regions of the neocortex on the one hand, and the basal ganglia, pretectal region, tegmentum and pons, on the other, were demonstrated. A revision of the earlier construct was accordingly undertaken and at present neocortical components and their related corticofugal fibers are generally viewed as integral to the extrapyramidal system.[45,52,53] Beyond this, considerable disparity of opinion is apparent.[42,110,165]

Von Bonin,[148] for example, in 1950 enumerated the extrapyramidal nuclei as follows: neocortical components (including the suppressor strips), inferior olives, cerebellum, nucleus ruber, substantia nigra, corpus subthalamicum and globus pallidus. He expressed some doubt as to whether the caudate nucleus and putamen should be included, and in this regard differed with many authors who confidently include the neostriatum.[14,17]

In addition to the nuclei just mentioned, the following have been looked upon by various authors as parts of the extrapyramidal system:

Tectum of midbrain (origin of tectospinal tract)
Vestibular nuclei (origin of vestibulospinal tracts)
Reticular formation (origin of reticulospinal tracts)
Pontine nuclei (receiving corticopontine tracts; origin of pontocerebellar fibers)
Lateral reticular nucleus
Lateral, dorsal and deep tegmental nuclei
Zona incerta
Interpeduncular nucleus
Interstitial nucleus (origin of interstitiospinal tract)
Nucleus of ansa lenticularis
Nucleus of ansa peduncularis
Pretectal nuclei of Cajal and Darkschewitsch (contributing to medial longitudinal fasciculus)

Lateral nuclei (ventrolateral) of thalamus (receiving dentatorubrothalamic fibers; origin of thalamostriatal and thalamofrontal fibers)

Measured in terms of the orthodox definition, a neural structure seemingly qualifies for inclusion in the extrapyramidal system provided it is an efferent mechanism and not pyramidal.[53] It is proper to raise the question, however, whether the mere sharing of such arbitrary characteristics warrants the assertion that all such structures constitute a *system*. To this pertinent issue we shall shortly return.

(b) *Physiologic Considerations*: As we have seen, certain functions were early imputed to the pyramidal system, namely, the mediation of voluntary and eupractic "phasic" movements. When in the course of time the extrapyramidal system was "discovered," its authors seemed to find in it functions different from if not frankly antithetic to those of the pyramidal system. These may be briefly summarized as follows:

1. Providing the organism with a coarse, tonic background of unlearned, involuntary muscular activity upon which the finer, discriminative, learned and voluntary movements of the pyramidal system play.
2. Mediating automatic associated acts.
3. Inhibiting actions of the motor system.
4. Effecting a high type reciprocal innervation of opposing groups of skeletal muscle.
5. Acting as a servomechanism which supports the "steering" of the final common pathway by the pyramidal system.

It is as if one were to have said, "The labels for the two anatomic systems are mutually exclusive; therefore, their functions must be so."

We shall now find it profitable to consider in detail the implications of one of these extrapyramidal functions – that concerning the tonic background, in which the pyramidal system is supposed to play no role, or at most a negligible one: "Although there may be some tonic innervation playing upon the final common pathway via the pyramidal tract, this neural mechanism is not particularly concerned with the control of tone." [56]

Against such dissembling statements stand the empirical observations (a) that section of the medullary pyramids in the cat, monkey and chimpanzee and (b) that ablation of the precentral and postcentral gyri bordering on the rolandic fissure (the pyramidal cortex) regularly diminish muscle tonus in the contralateral limbs and not infrequently render them flaccid.[22,36,52,83,131,2143,144] Just how these data can be interpreted to mean that in normal circumstances the pyramidal system "is not particularly concerned with muscle tone" is unclear.

In point of fact, sober consideration of the available evidence bearing upon separate phasic and tonic mechanisms should have prepared us for disappointment in our search on these grounds for differences in the pyramidal and extrapyramidal systems. It will be recalled that during the period 1912-27 evidence adduced by Ramsey Hunt[68,69] and Hunter, Latham and Royle[70,71,

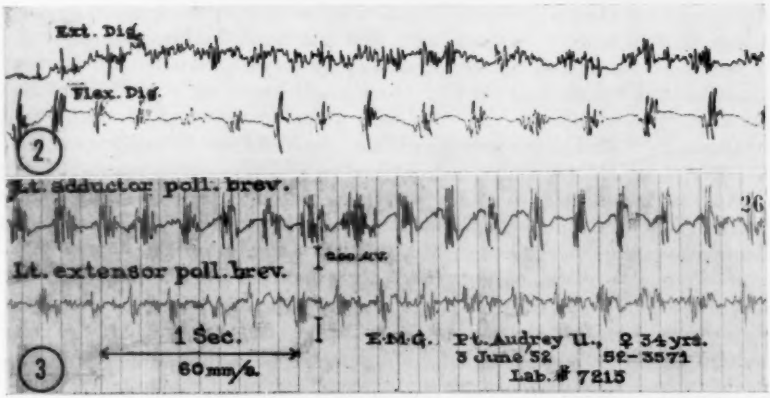


FIG. 2. Electromyographic record of hyperkinetic activity in a female exhibiting an athetoid dystonia. Surface electrodes overlying extensores digitorum (ext. dig.) and flexores digitorum (flex. dig.) muscles of the left forearm. Note relatively sustained activity in extensors during this run. In contrast, the flexors exhibit irregularly spaced bursts of action potentials. The principle of reciprocal inhibition appears for the most part severely violated. (Kindly loaned by Dr. Ernst Herz.)
FIG. 3. Electromyographic record of hyperkinetic activity in a female exhibiting left hemiparkinsonism. Surface electrodes overlying the left adductor pollicis brevis (lt. adductor poll. brev.) and left extensor pollicis brevis (lt. extensor poll. brev.). Note regularity of pattern and alternating burst of action potentials in protagonist and antagonist muscles. The principle of reciprocal inhibition is closely observed. Compare with figure 2.

[72,135] was interpreted to mean that qualitatively different neuro-effector mechanisms mediate the tonic and phasic activities of the organism. The effectors of myotonus and hypertonus (spasticity) were said to consist of red striated muscle fibers innervated by sympathetic nerves. The basal ganglia were considered prominent, if not the dominant, suprasegmental agents for regulating postural tone. Contrarily, the effectors of phasic movements were said to consist of white striated muscle fibers innervated by cerebrospinal nerves. The voluntary motor cortex was here regarded as the dominant suprasegmental agent for postural assumption (phasic action). Although this doctrine possessed the virtues of simplicity and teachability, it soon became suspect and within a few years its peripheral aspects were successfully controverted by Wilkinson[160] and Tower.[142] Haäggvist[58] endeavored to reopen the case in 1940, but failed to produce unequivocal evidence of separate FCP's for phasic and tonic impulses.[81,145,146] The central suprasegmental aspects of the doctrine, however, did not collapse for this reason and, for want of empirical evidence to the contrary, they remain with us by default rather than by virtue of positive operational demonstration.

It is to be borne in mind that, considered both temporally and spatially, phasic and tonic activities vary in degree over wide ranges. Overlap is everywhere evident, to such an extent that the difference between a relatively slowly executed phasic act of short excursion and a briefly sustained tonic postural set is more apparent than real. All in all, the case for separate supra-

segmental mechanisms subserving tonic and phasic activities does not appear strong. Even if it were, however, our difficulties would be far from resolved, for we should then be obliged to explain how the rapidly executed movements of chorea and ballism and the slow, tonically-laden movements of athetosis and dystonia musculorum can each arise from derangement of the extrapyramidal system. The theories offered thus far [8,9,19,115,154,155] fail to meet all pertinent facts.

It might be objected, of course, that since the above-mentioned abnormal movements resemble phasic activity only superficially, no real difficulty exists. Electromyography in choreatic, athetotic and dystonic movements certainly reveals frequent violation of the principle of reciprocal innervation (figure 2) in contrast to the regularity with which the principle is observed in normal phasic movements.[62,63] But unfortunately the honoring or dishonoring of this principle does not provide a very useful basis for distinguishing between pyramidal and extrapyramidal phasic movements, for in the alternating tremors of parkinsonism and myorrhythmia, which, like the abnormal involuntary movements of chorea, athetosis and so on, are considered to arise from derangement of the extrapyramidal system, reciprocal innervation is extremely well observed; no less so, indeed, than in normal phasic activities (figure 3).

At this point we appear to be confronted by a paradox. If, as now seems compelling, we are unable to assert precisely what is meant by the term pyramidal, how can we feel confident that those portions of it which remain unidentified are not at least in part extrapyramidal? And if we cannot be sure on this score, how can the conditions called for in our equation, $P \cdot E = O$, be satisfied?

In graphic retrospect, we may review what occurred historically by imagining a simple parallel situation – that of a gardener who, with something more than a pragmatic eye, thoughtfully contemplates the lawn he has been caring for and notes that one of its conspicuous features consists of blades of grass and the roots and seeds immediately identifiable with them. He gives this abstraction a convenient name, say, the "grass system." Further observations make it apparent that the lawn is not completely accounted for by the "grass system." The gardener now carefully surveys what is left and identifies the soil, the water, minerals and other organic matter in it, weeds, pebbles, rocks, twigs, worms, ticks, animal droppings, and so on. These are certainly parts of the lawn, but they are obviously not grass and in the gardener's view cannot be considered part of the "grass system." Without perceiving the necessity of first clarifying what he means by the term "system," he once again exercises verbal magic and comes up with a second ingenious formulation: the "non-grass" or "extra-grass" system.

Flushed thus with the joy of intellectual achievement, he goes beyond his morphologic constructs. Having assigned a function or set of functions to the "grass system," he feels the necessity for symmetry in his schema and assigns a function or set of functions to the "extra-grass system." In proceeding along

this line of thought he is unwittingly channelled by long-established linguistic habits, for in the labels, "grass" and "non-grass," there is an implied dichotomy. Consequently, whatever he says about the functions of one system cannot, in virtue of the mutually exclusive character of the symbols he has inadvertently adopted, be true of the other.

This is, after all, a not uncommon fallacy. Unless the student remains continuously aware of the relationship between his language habits and evaluations on one hand, and his interpretations of what he observes on the other, he is likely to assume that because one agent plays thus-and-such a role, another cannot or does not. All too often, he imputes to one agent and to that alone what may in fact, be ascribable to many.

In view of this, we are obliged to consider whether the dichotomy conceived to exist between the pyramidal and extrapyramidal systems is wholly warranted. A second possibility likewise merits attention: that, in fashioning the concept of an extrapyramidal system, our neurologic forbears unwittingly encompassed several disparate systems. But before we attempt to weigh these possibilities, we had best complete our original plan to measure the several terms of our definition against the Boolean equation.

"EFFERENT MECHANISMS" AND "MOTOR ACTIVITY"

The extrapyramidal system, we are told, embraces "all efferent mechanisms . . . . which have to do with . . . . motor activity." These expressions require critical analysis and we may begin by asking whether any operational meaning attaches to the familiar term, "efferent mechanisms."

It seems safe to assert that, if the extrapyramidal system exists at all, it consists in essence of a complex network of internuncial neurons located somewhere between an input made up of exteroceptive and proprioceptive fibers and an output made up of FCP's innervating the somatic musculature – probably more proximate to the latter than to the former. But between the input and output, just where does the system begin?

Among internuncial neurons, any particular nerve fiber may, depending upon the neural structure toward or away from which it conveys impulses, be regarded as both afferent and efferent. There is nothing in the fibers themselves (for example, tectospinal, rubrotegmental and vestibulospinal tracts, nigrostriatal fibers, and the neurons of the ansa lenticularis) which compels an either-or label. Accordingly it constitutes a highly arbitrary procedure for an investigator, working backward from the FCP, to decide how far upstream in the internuncial complex he is willing to travel and still continue to regard a given neuron as efferent. For him to break into some point along the course of the internuncial circuits, to characterize all components beyond this as "efferent . . . . having to do with motor activity" (and by implication to deny such characteristic to all antecedent components), to exalt the aggregate of all "efferent mechanisms" so designated to the status of a "system" (whatever that term means), and to impute to the latter organismic roles not subserved by other "systems," appears on the face of it a *modus operandi* as gratuitous

as it is sterile. Not its least result is to rob the term "efferent" of the discreteness of meaning that makes for useful scientific delineation.

The reader may ask, "But can we not decide what is 'efferent' by appeal to the morphology of neurocytes, for example, those we call the 'motor-type' cells of the caudate nucleus, the globus pallidus, the pars magnocellularis of the red nucleus, and the pars compacta of the substantia nigra?" The answer is that such appears at present extremely unlikely. This morphologic criterion itself is but another oversimplified neurologic construct. It has been arrived at by the exercise of what Huxley would have termed "selective ignorance"—the polarizing (in verbal terms) of items which actually exhibit transitional forms of every description and which should more accurately be represented on a continuum. Lassek[90] has emphasized that even for Betz cells no reliable morphologic criteria exist and Sprague[139] has recently asserted that the ventral horn cells in the spinal cord of the monkey cannot be classified functionally in terms of their topographic or morphologic relations.

Current ideas as to what constitutes a motor-type cell rest in large measure upon analogy rather than direct operational proof and, as the history of science eloquently reveals, analogy certainly does not provide an infallible guide. More specifically, we do not know that all cells having thus-and-such a form will, when stimulated, prove to be motor cells in the sense that they effect an observable modification of motor behavior; nor do we know that all cells lacking such form will, under similar circumstances, fail completely to alter motor behavior. To assert that, wherever found, motor type cells (and no others) produce motor effects and, conversely, that any observed motor effect must be incited by the activity of motor type cells (and no others) is to stumble headlong into the logical error of *petitio principii*. Currently available evidence simply does not support it.

But let us for the sake of discussion assume that a clear-cut distinction can be made on morphologic grounds between motor and non-motor cells. What would be its impact on our current notion of the extrapyramidal system? It would promptly exclude a number of components now considered by many investigators integral to the system, for example, the smaller multipolar cells of the inferior olives, substantia nigra, globus pallidus, red nucleus, putamen, caudate nucleus and "premotor" cerebral cortex, and the plenum of fibers coursing to and from them, such as thalamostriatal, nigrostriatal, striopallidal, tegmentoolivary, subcallosal fasciculus, and many similar elements. Is this what is ultimately intended for the system? And if so, shall we not in its ultimate realization find ourselves clasping a verbal phantom to our scientific breasts?

The problem cannot be any more easily settled by appeal to physiology. There is at present no known method of selectively stimulating or destroying *in situ* all or most of one kind of cell in a given nucleus, for example, the motor type, to the exclusion of its fellows, the non-motor type cells. Much less do we have assurance that the mode of stimulation employed in experimentation very closely accords with the circumstances of excitation, inhibi-

tion, suppression, and extinction that occur physiologically.[153] But if such were possible, our criterion concerning efferent mechanisms would once more compel us to exclude from the extrapyramidal system all neurocytes whose stimulation and destruction results in no observable alteration of motor activity. Again we should find ourselves embracing a verbal abstraction without phenomenal counterpart.

Arbitrary exclusion of this sort carries dangers of its own. We need only recall that in 1914 Wilson,[162] employing the crude physiologic technics then available, failed completely to evoke a motor effect by stimulating the neostriatum and concurred with L. S. Minor[122] that the structure mediates no motor function; yet, 25 years later, Mettler, Ades, Lippman and Culler[111] demonstrated a very palpable effect (the arrest and/or melting away of movement) by stimulating the neostriatum simultaneously with the cortex of the unanesthetized cat via implanted electrodes, and Rioch and Brenner[134] evoked running movements.

"... WHICH HAVE TO DO WITH MOTOR ACTIVITY"

Presumably, the pyramidal and extrapyramidal systems are alike in one major respect, namely, that both are "efferent mechanisms" and "have to do with motor activity." But if the conventional definition of the extrapyramidal system intends by this token to endow the system with distinctive characteristics, the question immediately arises, "What neural elements with central connections do not have to do with motor activity?"

By way of reply let us recall two fundamental assumptions regarding the nervous system. One amounts to a special case of the first law of thermodynamics, namely, that as part of the physical universe the nervous system is subject to the law of conservation of energy and matter. The other holds that the organism has but two ways of responding to the moiety of intra- and extraorganic stimuli that assail it: (1) by modifying the current activity of its glands; and (2) by modifying the current activity of its muscles. Under all conditions (except those of artificial experimentation, in which more or less isolation is arranged) these go hand in hand. Now, if these assumptions be accepted, we are bound to recognize that in a very rigorous sense the input of exteroceptive, proprioceptive and interoceptive fibers and all internuncial neurons disposed between them and the motor FCP's ultimately "have to do with motor activity." As such, these components qualify under our definition for inclusion in the extrapyramidal system with claims no less legitimate than those of the more orthodox efferent constituents. In such case, the combined extrapyramidal and pyramidal systems would be virtually synonymous with the entire suprasegmental apparatus of the nervous system and a not inconsiderable portion of the segmental.

Indeed, the only apparent exception to this statement would be the visceral neurologic structures of the central nervous system and the interoceptive impulses engendered by the viscera. Even here, however, the exercise of arbitrary powers of exclusion threatens to invite other difficulties, for, as experi-

mentation and clinical observation amply testify, the visceral activities of the (intact) organism appear every bit as capable as the somatic of influencing the phasic and tonic activities of striated muscle.[23,24,76,101,141,167] The fact that those portions of the neocortex from which visceral activities can most readily be modified correspond closely to those from which somatic responses can be readily evoked[29,50,136] provides further testimony of functional overlap.

CLINICOPATHOLOGY OF THE EXTRAPYRAMIDAL SYSTEM

As we have seen, data concerning relationships among (a) the anatomic course of the pyramidal system, (b) sites of lesion and/or experimental stimulation, and (c) those disturbances of behavior called the motor signs of pyramidal disease or upper motor neuron signs were acquired prior to the development of the extrapyramidal concept. A review of the relevant period of medical history indicates that, in a strictly negative or non-pyramidal sense, such data unwittingly became the measure of previously acquired clinical data and, ultimately, the agency by which a new class of normal and abnormal phenomena called extrapyramidal was created. Reduced to its essentials, the story unfolded somewhat as follows.

At about the time Paracelsus assumed the chair of medicine and surgery at Basel in 1527, kinetic and tonic-paretic motor abnormalities, long familiar to the laity and rather loosely described in ancient medical writings up to that time, began to be subjected to descriptive differentiation. Paracelsus first separated *chorea imaginativa* and *chorea lascivia* from *chorea naturalis* along lines which closely correspond to the present day psychogenic-organic dichotomy. A century later, Francis de la Böe recognized tremor-at-rest. In 1686, Thomas Sydenham penned his now celebrated description of the *Chorea Sancti Viti*, and in 1751 Gaubius described propulsive movements. The next large gain came in 1817 when James Parkinson separated the "shaking palsy" from other involuntary movements. By the middle of the nineteenth century, Walters (1841), Dunglison (1842), Gorman (1846), and Lyon (1863) had recognized chronic familial chorea, and Hughes (1846) and Germain Sée (1850) had separated the chronic choreas from the more acute and self-limited forms. There then followed in quick succession the descriptions of Hammond on post-hemiplegic athetosis (1871), Huntington on hereditary chorea (1872), Westphal on the distinction between certain tremors, bradykinesias and dysarthrias and multiple sclerosis (1883), Merzbacher on chronic diffuse sclerosis (1885), Déjerine and Sollier (1888) on infantile bilateral athetosis with imbecility, Unverricht on myoclonic epilepsy (1891), Anton on double athetosis (1896), Oppenheim on dystonia musculorum (1911), and Wilson on hepatolenticular degeneration (1912).

Thus, by the time the twentieth century had well started, clinicians were familiar with a number of involuntary motor disorders which, taken together, appeared to possess one striking characteristic in common, namely, that of being unlike the pyramidal motor disorders (Strümpell[140]). With this premise, what seemed more reasonable than to suppose that they must be related to one another?

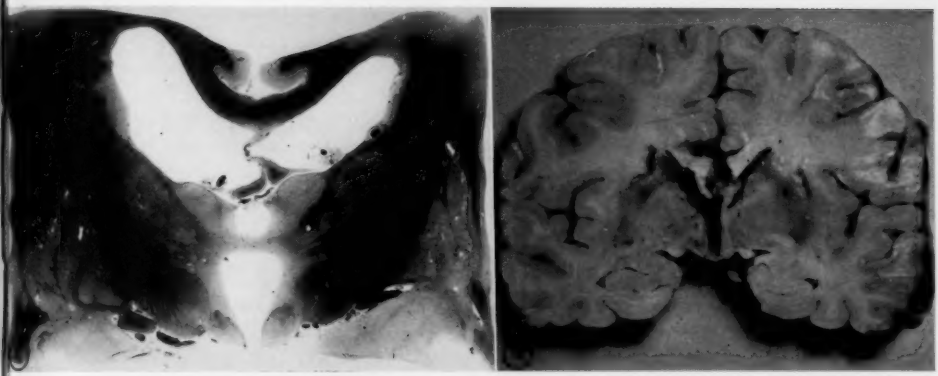


FIG. 4. Circumscribed encephalomalacia of the left putamen and globus pallidus, crus I and II, in an arterial hypertensive housewife aged 71 years. Clinically, the motor disorder conformed most closely to a vigorous hemiballism, a variety of hyperkinesia generally imputed to damage of the corpus subthalamicum rather than the lenticular nucleus. The corpus subthalamicum and its efferent pathways were in this case bilaterally intact. It is of interest that various authors have considered the lenticular nucleus *the* typical site of lesion in (*a*) chorea, (*b*) athetosis, (*c*) dystonia, (*d*) alternating tremor and (*e*) rigidity. (The histologic details of this case have been previously published.[118]) FIG. 5. Coronal section of brain of a 47 year old arterial hypertensive housewife who had had five "strokes" (syncopic episodes only) during the two years prior to death from acute coronary insufficiency and peripheral vascular collapse. Paranoid, apprehensive and hysterical on admission. No paralysis. Severe hypertensive retinopathy. At no time had hyperkinesia developed. The neostriatum exhibited long-established multiple infarcts bilaterally, with neurocytic outfall of moderate severity, glial degeneration, scarring and many gemistocytic astrocytes. No evidence of old or recent hemorrhages. The Willisian vessels revealed advanced arteriosclerotic and atherosclerotic changes. The left posterior communicating artery was congenitally absent.

Circumscribed pathologic counterparts or, more accurately, coexistent lesions of these non-pyramidal clinical disorders were likewise described. Aitken (1853) found the specific gravity of the corpus striatum diminished in acute infectious chorea. Broadbent (1866) and Meynert (1868) noted gross embolic foci in the same structures. In 1895 Anton provided microscopic evidence of damage to the basal ganglia in chorea. In a notable study Alzheimer asserted that, while choreatic lesions may indeed be conspicuous in the corpus striatum, the thalamus, hypothalamus, pontine region, dentate nucleus and cerebral cortex were also frequent seats of damage.

Opinion as to the seat of lesions responsible for paralysis agitans was long divided between the basal ganglia and optic thalamus (Oppolzer, 1861; Virchow, 1864; Leyden, 1864; Bouchut, 1879; M. Loewy, 1903). More intensive studies by Manschot (1905), Jelgersma (1909) and F. H. Lewy (1911 and 1912) emphasized that in addition to striopallidal damage the cerebral cortex, midbrain, medulla, hypothalamus, lateral thalamus, cerebellum and H_2 fields were commonly involved.

In 1876 Gowers described cicatrization of the right thalamus in an instance of left hemichoreoathetosis and was promptly confirmed by Lauen-

stein (1877) and Landouzy (1878). However, in 1879 Ringer held that athetosis is due to atrophy of the basal ganglia and this notion was supported by Hammond's report in 1890. Déjerine and Sollier (1888) found more extensive lesions in their case of bilateral athetosis.

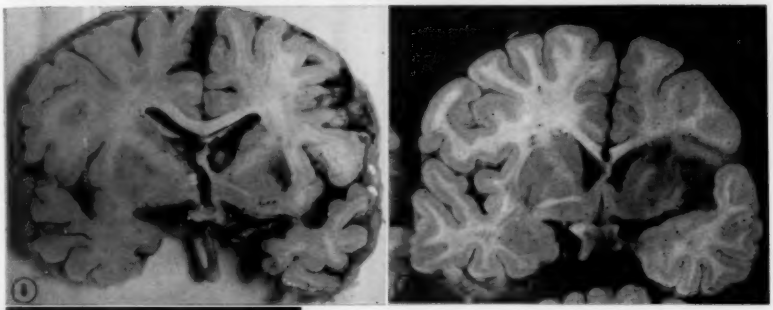
In 1883, Greiff described damage to the corpus Luysi in connection with a disorder later to be called ballism. The significance of this observation was not fully appreciated until 1923. Meanwhile, Oppenheim and Vogt[126,127] (1911) had described *état marbré* of the basal ganglia in a case of double athetosis, and Wilson[161] (1912) had reported damage to the lenticular nucleus in a motor disorder which closely simulated cases previously described by Westphal and Strümpell.

Given the new premise, that the non-pyramidal clinical disorders are related, it must have seemed compellingly logical to suppose that the neural structures in which coexistent lesions were found must also be related, very likely in the manner of a system. At first this notion was but vaguely formulated but in time (and with enough reiteration) it became sufficiently well crystallized to permit Foerster to assert that "a discrete motor syndrome corresponds to the destruction of a discrete, functional, unitary anatomic system."

From 1918 on,[86] the term "extrapyramidal" began to appear with increasing frequency in the medical and biologic literature and following the 1923 publications of Jakob[75] and Lewy[96] the system was confidently asserted to possess its own anatomic makeup, physiologic attributes and clinical pictures. The individual signs and symptoms of the clinical pictures were likewise regarded as expressions of disorder of the extrapyramidal system, and with this step the circle of reasoning was securely closed. In conceiving a positive relationship to exist among motor disorders which exhibited in common the negative feature of being non-pyramidal, the verbal magician had in effect put a rabbit into a silk hat; henceforth, the investigator reaching into the hat was certain to bring the furry creature forth. To this *modus operandi* no audible objection was raised.

Our inquiry has by now revealed a sufficient number of faults in logic to cast doubt on the validity of the conventional extrapyramidal map. But, it might be protested, the inquiry has chiefly spelled out defects in the process of making the map; there still remains the (slender) chance that the extrapyramidal formulation as an intuition is serviceable – in the sense in which a student might reach the correct answer to an arithmetic problem despite the commitment of intermediate errors. This possibility must be acknowledged. Indeed, we might yet retain the map if it provided investigators at clinical and basic science levels with useful and self-consistent guides, that is, with realizable predictions. Unfortunately, as the following observations document, it does not.

1. Circumscribed lesions, assertedly confined to a particular anatomic structure, for example, the globus pallidus, putamen and caudate nucleus, have been held responsible by different authors[1,26,30,32,42,44,62,68,75,80,158] for several different clinical varieties of hyperkinesia: dystonia, athetosis, chorea, spas-



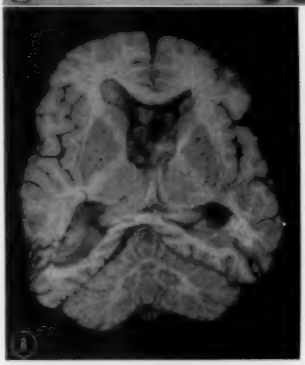


FIG. 6. Coronal section of brain of a 78 year old male who died of bronchopneumonia nine days after transurethral resection for benign prostatic hypertrophy. This section passes through the anterior limb of the internal capsule at the level of the anterior commisure. The patient had had a "light stroke" (syncopic episode) several months prior to admission, not followed by paralysis. He had been moderately confused for two years prior to death, but capable of performing many household tasks. At no time did hyperkinesia or hypertonicity develop. A brownish infarct of the left putamen, manifestly a lesion of long standing, fairly selectively involved the entire nucleus. Microscopically, neurocytes and myelinated fibers within this lesion were disintegrated. Many monocytic and gitter cells containing light brown pigment granules were present. The brain tissue bordering upon the necrotic putamen showed a decrease in neurons. Many of the remaining neurocytes were undergoing neuronophagia. Microglia and astrocytic proliferation were apparent. The cerebral blood vessels were generally atherosclerotic and the cortex showed mild generalized evidences of atrophy. FIG. 7. Coronal section of brain of a 41 year old governess, afflicted since childhood with rheumatic heart disease. This section passes through the anterior limb of the internal capsule at a level just behind the optic chiasm. Death occurred from ventricular fibrillation during mitral commissurotomy. The cerebral infarct in the right hemisphere is the result of a "stroke" (embolism?) which occurred seven years before and which resulted in a left hemiparesis from which a nearly complete clinical recovery had been made. At no time did hyperkinesia develop. Two years before death a moderately severe "thalamic hyperpathia" ensued. The encephalomalacic lesion shown above was yellow-brown in color and contained multiple small cysts. Microscopically, it exhibited a severe outfall of neurocytes, glial degeneration and repair, and many swollen gitter cells. Serial sections revealed implication of the following: (1) the dorsal portion of the caput and corpus (and, more posteriorly, the entire cross section of the tail) of the caudate nucleus; (2) the dorsal and, more posteriorly, the mid- and dorsal portions of the putamen; (3) portions of the anterior limb of the internal capsule. (The posterior limb largely escaped damage); (4) the external capsule, claustrum and island of Reil; and (5) the lateral thalamic nuclei at the level of the massa intermedia. FIG. 8. Horizontal section of the brain of a 43 year old machinist in whom the syndrome of slowly progressive right hemiparkinsonism had existed for ten years. A circumscribed oligodendroglioma of the septum pellucidum impinges upon both caudate nuclei and implicates the genu of the internal capsule and the anterior nuclei of the thalamus. Death came suddenly without premonitory clinical evidences of brain tumor. The autopsy findings other than those in the brain were non-contributory. Microscopically, a considerable outfall of neurocytic and glial elements was apparent at the region of juncture of the caput and corpus of each caudate nucleus and of the anterior and ventral anterior nuclei of the thalamus. The basal ganglia otherwise appeared intact. The involved structures have seldom been held to be *the* sites of lesion in parkinsonian tremors. (Courtesy of Dr. Richard Grimes, Medical Examiner, City of New York.)

modic torticollis, ballism, alternating tremor, and so on. It does not appear likely that all these rival claims can be simultaneously correct.*

2. Clinicopathologic data is at present insufficient to warrant the belief that for each clinical variety of hyperkinesia, for example, chorea, athetosis, dystonia, alternating tremor, and so on, a particular neural structure or neural complex will regularly be found damaged [14,31,32,55,59,68,69,77,85,100,102,104,105,133] (figure 4).

3. The demonstration at necropsy of a lesion in a particular neural complex (for example, the paleostriatum, neostriatum, pretectal region, suppressor strips, and so on) does not permit a conclusion on the part of the prosector that a hyperkinesia of any kind must have been present during life; much less does it permit a conclusion as to the clinical variety of motor disorder that must have been present[7,10,31,32,38,85,133,137,149] (figures 5, 6, 7 and 8).

When the clinicopathologic data upon which the extrapyramidal concept rests are disinterestedly re-examined, it becomes evident that the emphasis has far too often been placed upon likenesses and that differences and exceptional cases have been lightly discounted.

The available evidence being inconsistent and in many cases frankly contradictory, the investigator is obliged to entertain the possibility that such pathologic lesions as are at present held responsible by different authors for particular varieties of hyperkinesia may constitute mere coincidences, or at least may not be directly and solely responsible for particular varieties of hyperkinesia. To assume that a brain lesion exhibited at autopsy, even if oft-demonstrated, provides *per se* a sufficient explanation of clinical phenomena observed during life is to fall naively into the *post hoc* error. Even if the data were thoroughly consistent in both positive and negative senses, current scientific notions of multifactor causality should impose upon the critical student a considerable reservation as to the completeness of such account. Our current methods of pathologic investigation are relatively crude. It is not unlikely that histo-cyto-microchemical and biophysical methods now in process of development will some day disclose subtle pathologic changes far beyond our present capacity for imagination. At such time, many of our current pathogenetic concepts may appear to have been misleading.

PHYLOGENETIC DATA

A question is now in order as to whether or not the prevailing pyramidal and extrapyramidal dichotomy receives inferential support from phylogenetic data. Was there not, in the course of evolution, a time when no pyramidal system existed; when the highest suprasegmental components of the nervous system corresponded to what we presently designate as the extrapyramidal system? And if so, did not the advent of the pyramidal system in the animal

*One possible account for these disparate views is a lack of basic nosologic agreement, for example, as to the precise circumstances in which the terms chorea, athetosis, ballismus, and so on, apply. But nosologic difficulties certainly cannot account for all such disparities. The well-patterned tremor of parkinsonism can hardly be confused with the non-patterned movement disorders; yet, the same anatomic structure has been incriminated by different authors in the pathogenesis of these hyperkinesias.

series then constitute a new element, one clearly disparate with regard to the pre-existing structures? As a possibility, this cannot be summarily dismissed. However, such phylogenetic evidence as we possess does not permit so simple a resolution of the problem.[4,5] Whatever antedated the pyramidal system in a phyletic sense was certainly not synonymous with the extrapyramidal system as currently conceived. Comparative anatomy and paleontology suggest that as the rhinencephalic telencephalon (allocortex) slowly engendered the neopallium and, over the course of time, eventually a pyramidal system, it engendered simultaneously certain subcortical ganglia (for example, the neostriatum and claustrum) and numerous non-pyramidal neocortical elements which we count today among the integral parts of the extrapyramidal system. Concomitantly, and probably in large measure influenced by the same telencephalizing factors responsible for this quickening, the pons and lateral lobes of the cerebellum were markedly expanded. In this phyletic process we search in vain for evidence of a clear-cut dichotomizing of pyramidal and extrapyramidal systems.[14,42,106] Man's verbal dissections of nature do not appear in this instance to conform very closely to her operations, which recalls Johnson's[78] observation that man is the only animal who can talk himself into troubles that would not otherwise exist.

DISCUSSION

The pyramidal tract, from which the name of a so-called neural system has been derived, seemingly includes a number of neural elements which cannot properly be considered parts of the pyramidal system. For this and other reasons already mentioned, the pyramidal system appears to be an uncertain concept. By the same token, the extrapyramidal system, which by definition depends for its claim to anatomic and physiologic discreteness upon being non-pyramidal, appears similarly uncertain, if not largely fanciful. Of even greater significance is the fact that clinicopathologic and experimental findings cannot readily be reconciled with current anatomic and functional concepts of the so-called pyramidal and extrapyramidal motor systems.

This may mean that the extrapyramidal concept is but a term for a high-order abstraction, referents for which are not demonstrable in the phenomenal world. If so, and provided that its usage in this sense were generally appreciated, there could be no serious objection to its retention in neurologic jargon, for science abounds in and advances by just such "as-if" formulations, for example, neutrons, mesons, atoms, molecules, genes, entropy, negative acceleration, imaginary numbers, and so on. The chief requirement of all such verbal maps is that they should continue to aid the investigator in his efforts to get about in the territory they represent. By this measure, the extrapyramidal concept has not proved susceptible of meaningful analysis and should, therefore, come under suspicion. In a word, we are now called upon to decide whether or not we are dealing with a myth.

It may also mean that under the term, "extrapyramidal system," our neurologic forebears unwittingly lumped together a number of genuinely discrete

but unidentified neural systems, the differences between which are comparable to those now presumed to exist between the pyramidal and extrapyramidal systems. Here, we have to try to decide whether or not we are merely oversimplifying organismic processes. Magoun and Rhines,[103] in speaking of the extrapyramidal systems, appear to be probing in this direction.

Again, it may mean that the unvoiced assumption which is fundamental to both the pyramidal and extrapyramidal concepts, namely, that there can be in the living organism such an entity as a motor system (as distinguished from a sensory system or a secretory system, for example), is invalid. Elliott[42] speaks of a motor system, but feels impelled to deal with it as a whole rather than to envision pyramidal and extrapyramidal systems subserving specific types of response. Here we are required to decide whether or not an act of faith which happens to fall in line with our established predilections is being practiced.

Other possible meanings might, of course, be cited. But whatever the final account(s) of our current confusion may be, it is clear that an appreciable revision of current neurologic maps must soon be implemented.

A first move toward such revision would be to discontinue the current linguistic practice of referring to neural structures, functions, clinical signs, symptoms, syndromes and diseases as those of the pyramidal or extrapyramidal system. Such a move would in no way detract from established factual data, compromise description, or incur measurable penalties in the domain of theory or practice. At the same time we should seriously attempt to clarify certain well entrenched notions, particularly those symbolized by the terms "voluntary," "involuntary," "organic," "functional," and so on.

A second move would be to recast current nosology so that physiologic and clinical phenomena might be capable of description in terms generally agreed upon by qualified students. Abnormalities of phasic activity and myotonus, for example, might be subjected to thorough review, making use of the traditional methods of clinical observation and the newer methods of precision (slow motion cinematographic analysis, electromyography, electrophysiology of peripheral nerves, cortical and subcortical structures, ergometry, and the several pertinent pharmacologic tests) introduced since the phenomena were first described. The terms "hyperkinesia," "akinesia," "hypokinesia," "hypotonus," "hypertonus," and so on might then be fruitfully employed, singly or in combination, in describing clinical phenomena and could be modified by as many relativistic adjectives as dictated by the need for precision, for example, "regular", "irregular"; "patterned", "non-patterned"; "repetitive", "non-repetitive"; "rhythmic", "non-rhythmic"; "adaptive", "non-adaptive"; "conformance" and "non-conformance" to the principle of reciprocal innervation, and so on. The temporal and spatial characteristics of all such phenomena, the ranges within which they vary diurnally, and the biosocial circumstances in which they appear or regress might likewise be noted.

The operational counterparts of all such modifiers should, of course, be matters upon which agreement has been reached by qualified students of the

subject. All this could probably be most satisfactorily realized in a conference which provides an unhurried, warm and permissive atmosphere and in which full opportunity for pluridirectional communication among those present is available. The qualifications required of participants might include (a) technologic experience in the pertinent areas of biologic and medical science, (b) a capacity for listening, and (c) clear awareness of and a readiness to employ scientific method.

Once harmonious agreement has been reached as to what the terms "chorea", "athetosis", "dystonia", "tremor", and so on denote in a descriptive sense, the task of cataloguing the loci of all brain lesions found associated with the several disorders should receive extended critical attention. The search in each case would have to be eminently thorough and standardized. The currently available physiologic, chemical and pathologic technics should be exploited to spell out negative as well as positive findings. Finally, case studies should be pooled and dispassionately examined by a body of designated qualified observers, and when a sufficiently large series had been acquired the data should be subjected to statistical analysis. Through the employ of such measures we might look forward with optimism to an ever more precise comprehension of the pathogenesis of the kinetic and tonic aberrations of the organism and to the eventual disclosure of order in what now appears to be disheartening chaos.

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Recent Experimental Studies on Pain and Analgesia

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In an extremely interesting and provocative paper, Beecher[2] recently pointed out some important differences between "clinical" and "experimental" pain and the divergent results that are frequently obtained by use of different analgesic testing methods. While there can be no doubt that, for the clinician's purposes, the results of direct clinical measurements of pain and analgesia are crucial, it is nevertheless also true that such methods are difficult and can be carried out only in institutions with special facilities. Therefore, experimental methods of measuring pain and analgesia continue to be of importance, both from the standpoint of theory and of the practical needs of pharmacologists and others who are responsible for the development of new methods for alleviation of pain.

The present report is an attempt to analyze the reasons for divergent results obtained by different analgesic testing methods, and to indicate the necessity for a broad approach to the problem of pain and its relief. This analysis proceeds from an "operational" point of view, that is, the meaning of a statement about data of observation is to be sought in the procedures which the observer carries out.[4,30] Application of this principle reveals that the terms "pain" and "analgesia" refer to a variety of phenomena, depending on the technics employed by the observer and the situation which obtains when the observations are made. Thus Beecher's clinical method involves the use of patients in a large, well-staffed institution who are recovering from surgical procedures for the treatment of illnesses with good prognosis, and the assessment of pain on the basis of two criteria: the verbal report of the patient and the observer's opinion regarding the patient's degree of comfort.[21] In contrast, experimental methods in human subjects involve the use of healthy individuals, with varied expectations and relationships to the experimenters, who are subjected to unfamiliar stimuli of different sorts (thermal, electrical, mechanical, or chemical) which are applied to various organs (skin, teeth, viscera, muscles). The pain experience evoked by such procedures has been reduced to two components—perception and reaction,

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in keeping with traditional mind-body dichotomies. Actually, both refer to a variety of organismal responses to nociceptive stimuli. Thus, perceptions are defined by measurements of thresholds and intensities of painful stimuli, based on verbal responses of quite different sorts; reactions are defined by measurements of skeletal motor withdrawal responses, autonomic changes, or alterations in goal-directed performances. In animals, similar stimuli have been employed, but of necessity only reactions are available for measurement. It will become apparent later that all of these organismal responses to nociceptive stimuli can be dissociated from one another. Hence they are not to be regarded as equivalent or causally related to each other.

However, experience has shown that, for the purpose of predicting analgesic potencies of drugs, these experimental methods are useful within certain limits.[29] Thus, thresholds of perception of painful radiant heat stimuli are elevated by opiates in trained subjects,[11] but not in untrained individuals.[11,8] Even in trained subjects, acetylsalicylic acid produces, at most, very small elevations of pain perception thresholds, and, contrary to clinical experience, the maximum analgesic effect demonstrable by this method is obtained by administration of no more than 0.3 gm. of this drug.[11] Intensities of painful radiant heat stimuli are estimated at lower values after administration of morphine,[11] but whether or not this agent reduces the intensities of electric shock stimuli appears to depend on particular experimental conditions. Thus, it has been shown[14] that morphine exerts such effects if, prior to testing, no effort is made to alleviate apprehension of the subjects; under these conditions, the intensities of painful electric shock stimuli are overestimated by the subjects and morphine reduces this error. If, on the other hand, apprehension is allayed, such intensities are estimated accurately, and morphine has little or no effect on such judgments.

Although analgesics reduce the magnitude of changes in skin resistance which are induced by painful radiant heat stimuli,[11] this reaction is also depressed by small doses of barbiturates or atropine[19] which cannot be classified as potent analgesic agents. Also, pain may be relieved by procedures such as frontal lobotomy which do not elevate perception thresholds or skeletal motor withdrawal reactions to painful radiant heat stimuli.[6] A number of other reactions to painful stimuli have been used as indicators of analgesic drug effects in man. Most recent is a method based on the assumption, inferred from clinical experience, that anticipatory anxiety, or fear of pain, is an important aspect of the pain experience. It has been demonstrated that the performance of subjects who must react rapidly by pressing a key in response to a visual stimulus in order to avoid painful electric shocks may be profoundly disrupted by repeated shock penalizations for slow reaction times. Morphine reduces such anticipatory effects of previously administered shock penalties.[15] However, it remains to be shown that such effects are exerted only by administration of drugs or by clinical procedures which reduce pain.

Similar limitations have been encountered in animal experimentation. Up to the present time, such methods have utilized one or another unconditioned

reflex responses to painful stimuli as an indicator of the pain experience. These have been summarized in detail elsewhere.[10] Recently, two methods have gained wide popularity—the "flick" response of the rat's tail[7] and the "skin-twitch" response of the dog,[1] both evoked by radiant heat stimuli applied to appropriate areas of the skin. Both the "tail-flick" and the "skin-twitch" responses appear to be spinal reflexes, normally inhibited by supraspinal mechanisms.[16,18] A less widely used method is based on the "lip-twitch" response in the dog, which is evoked by electrical stimulation of the pulp of a canine tooth[23] and is integrated subcortically.[31] When such methods are employed, the analgesic effects of drugs are expressed in terms of elevation of pain reaction thresholds or reduction in magnitude of the response. Such effects appear to be due to direct depressant actions of analgesic agents and to augmentation of suprasegmental inhibition.[16,18] By use of these and similar methods, the prediction of the relative analgesic potencies of drugs in the opiate series has been fairly successful. However, they have not been useful in the study of milder analgesics such as acetylsalicylic acid.[5,9] Also, it has been shown that mephenesin reduces markedly certain reflex responses to painful stimuli,[12,16,17,20] yet this muscle relaxant cannot be compared with opiates in respect to its clinical analgesic effects. The possibility of utilizing anticipatory responses to painful stimuli as indicators of pain and analgesia in animals has not been explored sufficiently, although it is known that under certain conditions morphine reduces the magnitude of conditioned skeletal motor responses to electric shock stimuli.[25,29]

When the operations involved in the carrying out of these experimental procedures are analyzed and compared with those involved in the clinical evaluation of pain and analgesia, it becomes apparent that every method of measurement entails the exclusion of some factors and the introduction of others which modify the pain experience. There are differences in the subjects used, their expectations and previous histories, the integrity or modification of the organism studied, as well as differences in experimental arrangements, including the type of stimulus employed and the sort of response that is measured. Furthermore, such differences cannot be avoided, since scientific explanations of natural phenomena always involve modification of that which is to be explained, for the purpose of control and quantification. Hence, a given drug cannot be said to exert its actions through any single mechanism, or to have only one action under any and all conditions. Rather, it appears that drugs have certain ranges of effects under a number of well defined conditions, and that they exert such effects through a number of mechanisms. Prediction of the analgesic or other properties of a drug must be based, therefore, on a consideration of the pattern of its effects, delineated with a wide variety of technics in a number of experimental situations.[32,33] In other words, the genesis of pain and analgesia is multifactorial.

Accordingly, it may be useful to list some of the factors, expressed operationally as demonstrable correlations, that are known at present to contribute to the genesis of pain, and which may be modified by analgesic agents.

A. Physiologic factors (structure-function correlations).
   1. Relation of pain perception threshold to temperature of pain endings in skin.[11]
   2. Relation of pain intensity perception to delivered energy of electric shock stimuli.[13]
   3. Relation of quality and intensity of pain to fiber size and pattern of cutaneous stimulation.[3]
   4. Relation of intersegmental spread of pain and development of hyperalgesia to intensity and location of peripheral[11] or spinal[22] foci of nociceptive stimulation.
   5. Relation of internuncial neuron activity at various anatomic levels of integration to nociceptive stimulation.[24,27,28,29]
   6. Relation of supraspinal inhibition to magnitude of reflex responses evoked by nociceptive stimulation.[16,18]
   7. Relation of concern about pain to integrity of thalamofrontal fiber systems.[26]

B. Psychologic factors (stimulus-object correlations).
   1. Relation of previously induced pain to estimation of pain perception thresholds.[11]
   2. Relation of altered expectation (by suggestion) to perception of pain thresholds and estimation of pain intensities.[11]
   3. Relation of anticipatory anxiety to judgment of intensities of painful stimuli.[14]
   4. Relation of anticipatory anxiety to disruption of performance in a pain-avoidance situation.[15]

It can hardly be expected that a single analgesic drug will have potent effects on all of the factors listed, or that different analgesic agents will affect similar factors to the same degree. No doubt other factors that contribute to the genesis of pain and analgesia will be demonstrated by further research, but it is hardly likely that a single cause of pain and analgesia will ever be found. At least for the duration of the foreseeable future, it would seem that, in the search for new methods to alleviate pain, a multifactorial approach is likely to yield more fruitful results than adherence to one or another method based on preconceived notions of what is fundamental.

SUMMARY

1. Operational analysis of clinical and experimental methods of evaluating pain and analgesia indicates that discrepancies between the results of different methods of investigation are due, at least in part, to unavoidable differences in the constellation of factors that contribute to the data acquired.

2. Some factors are listed, in terms of demonstrable correlations, which appear to be significant in the genesis of pain and analgesia.

3. It is suggested that in the search for new methods of relieving pain a multifactorial approach be used, instead of any single method that is now available.

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Multiple Symmetrical Polyneuropathy Treated with Cortisone

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INDIVIDUAL case reports have suggested that corticotropin (ACTH) or cortisone may modify favorably the natural course of multiple peripheral neuropathy of unknown cause. Similar inferences have been drawn after hormonal treatment of patients with Bell's palsy and neuroparalytic accidents following rabies vaccine.

Seltzer and co-workers[1] gave ACTH to a 17 year old girl who suffered an acute polyneuropathy with elevated spinal fluid protein. Corticotropin was begun 14 days after neurologic symptoms began, a time when the patient was critically ill with partial ophthalmoplegia, facial weakness, paralysis of swallowing and quadriplegia. Neurologic improvement began within 24 hours of starting corticotropin, and recovery was complete in six weeks although the hormone was continued for only five days. Stillman and Ganong[2] noted marked improvement within 48 hours of giving corticotropin to a 59 year old man suffering from an acute symmetrical polyneuropathy which was associated with an elevated spinal fluid protein. On the twenty-fifth day of ACTH treatment, this patient suffered a neurologic relapse. It was concluded that he had become non-reactive to corticotropin, and cortisone was substituted. Further improvement ensued promptly and total recovery was achieved 24 days later.

Garrido-Lecca and Tola[3] treated with corticotropin a 40 year old woman in whom pain and weakness in the lower extremities, associated with headache and tremor of the hands, developed after the seventeenth of a series of rabies vaccine injections. ACTH was begun on the eleventh day of unremitting neurologic symptoms and continued for eight days. Considerable improvement was described within 48 hours and the patient was said to be almost normal at the end of the treatment period. Rothlender[4] and Robbins[5] have recorded unusually rapid amelioration of Bell's palsy following cortisone injections.

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In contrast to the above reports where improvement was seen in peripheral nerve disease subsequent to ACTH or cortisone administration, Shy and McEachern[6] observed no response to cortisone in three patients with multiple peripheral neuropathy of unknown cause. Merritt[7] stated that he and Glaser also obtained negative results in cortisone treatment of three patients with polyneuropathy of unknown cause. Although details were not given in any of these cases, two of Merritt's patients were said to conform to the Guillain-Barré type of peripheral neuropathy.

Further data is necessary to appraise the value of corticotropin and cortisone in disorders of peripheral nerves. The present report describes three patients with multiple and symmetrical peripheral neuropathy recently treated with oral cortisone at the U. S. Naval Hospital, St. Albans. The course of illness in these patients was dissimilar, and two of the subjects appeared to have developed polyneuropathy as a manifestation of hypersensitivity to penicillin, in itself an unusual reaction.

CASE REPORTS

Case 1.—A 28 year old woman had been delivered of a normal term infant by low forceps under nitrous oxide anesthesia on August 2, 1952. She was unusually fatigued following parturition, and this condition persisted. On August 18 she developed frontal headache which was followed the next day by generalized muscular aching and tenderness, as well as paresthesias of the hands and feet. On August 20 she noted that eye movements were painful. On the same day perioral paresthesias appeared and her temperature rose to 102° F.

When hospitalized on August 21 she had no fever and none developed subsequently. She was unable to walk or even sit erect unassisted. She had diplopia on far lateral gaze bilaterally, reduced sensation in the second and third divisions of both fifth cranial nerves, and fasciculations in both periorbital and perioral muscle groups. She was able to support the weight of her extremities against gravity only briefly, and had lost almost completely the ability to perform fine movements with her hands and feet. Her muscles were flaccid and extremely tender, and deep reflexes could be obtained only in the triceps and patellar tendons. The plantar responses were flexor and remained so. She had symmetrically reduced sensory discrimination to all testing modalities distal to points 10 cm. distal to the olecranon processes and distal to the inguinal ligaments. Position and vibration sense were impaired most prominently, the C128 tuning fork transmitting no sensation distal to either the mid-forearms or knees. The soles of the feet were hyperalgesic. The spinal fluid contained 168 mg. per cent of protein but was otherwise normal.

A nutritious diet and supplementary vitamins were given. Neurologic defects increased during her first ten days in the hospital. She developed reduced bladder and rectal sensations. Other sensory defects increased so that levels were observed 10 cm. above both olecranons and scattered response to pinprick was obtained up to the sixth thoracic dermatome, with loss of vibratory sensation to the sixth thoracic dermatome. She was unable to sit up, use her hands effectively, or raise her legs from the bed. Her muscles were so tender that she cried out with pain when moved for routine nursing procedures.

The spinal fluid protein rose to 214 mg. per cent on September 8 and to 304 mg. per cent on September 19. On September 20 and October 1, 100 mg. of BAL (2,3 - dimercaptopropanol) was given every four hours to a total of 600 mg. for each course. Except for pain at the site of injections, no alteration in condition was observed after this medication.

She continued to have severe pain, and motor and sensory disabilities remained maximal.

On October 7 she was started on oral cortisone, 300 mg. the first day, 200 mg. the next, and 100 mg. daily thereafter. The nature of the medication was not disclosed to her. She had been started on a placebo identical in appearance three days before without effect. Within 24 hours of ingesting cortisone her pain disappeared, she was able to sit up in bed unassisted, and was able to hold a drinking cup without spilling its contents. Two days later she was able to raise each leg one and a half feet from the bed and could perceive a tuning fork over her iliac crests. On the sixth day after starting cortisone she could raise herself to a sitting position, propel her own wheelchair, and feed and wash herself. Sensation was normal to testing down to 5 cm. below her left olecranon, to her right wrist, and to both knees. On the ninth day of treatment, except for the C256 tuning fork, sensation was found normal in the upper extremities and in the lower extremities down to the ankles. Spinal fluid protein was 256 mg. per cent. A placebo was substituted for cortisone the next day, and by night she complained that paresthesias had returned in her hands and had increased in her feet. She retained a sense of well being, however, which had returned when cortisone was first started, but failed to improve further during the next two weeks. On October 29 cortisone was again administered in a dosage of 100 mg. daily. Within 48 hours paresthesias disappeared and vibration sense returned to normal in her hands, and deep reflexes were perceptible in the triceps tendons for the first time since the week of admission. During the next four days she regained her ability to walk, though canes were needed for support. On November 11 she noted a sudden increase in strength, lost the paresthesias in her feet completely, and was able to walk and climb stairs unassisted. Neurologic examination was normal except for easy fatigue on test procedures and reduced perception to all sensory modalities below the malleoli. Spinal fluid protein was 150 mg. per cent. Cortisone was stopped the following day without apparent effect. She was discharged from the hospital. Four weeks later she still had residual reduction of sensation in her toes, but six weeks after discharge she felt well and had a normal neurologic examination except for deep tendon reflexes that were still generally reduced.

Case 2.—A 25 year old white male soldier developed a penile chancre on May 1, 1952. Dark field examination showed T. pallidum, and he was given injections of penicillin, 300,000 units twice daily, to a total of six million units. After the first penicillin injection he developed generalized urticaria which promptly subsided following an injection of epinephrine. On the tenth day of penicillin therapy the man complained of weakness and reduced sensation in the lower extremities. He then went AWOL when advised he was to have a spinal puncture, and was not re-examined until August 7, 1952. At this time he complained of weakness and paresthesias in all four extremities, and on examination was found to have profound weakness in both upper and lower extremities, with absent deep tendon reflexes and bilaterally reduced sensation to all testing modalities both in the fingers and distally to mid-calf levels. Spinal fluid contained 129 mg. per cent of protein and four lymphocytes. On this and all subsequent occasions both blood and spinal fluid gave negative reactions to serologic tests for syphilis.

He was given a course of BAL at his local medical dispensary. No improvement was observed, and he was transferred to St. Albans Hospital on October 24. At this time he walked with a high steppage gait. Moderate interosseus muscle wasting was detected in his hands and feet. He was just able to support the weight of his feet and hands against gravity and had moderately severe and diffuse weakness in more proximal muscle groups. Tendon reflexes were absent and superficial abdominal reflexes weakly present. He perceived sensory stimuli normally except in his toes, where position and vibration sensation were reduced. Spinal fluid contained 79 mg. per cent of protein and no cells. No improvement was noted during a one month observation period on a nutritious diet and vitamins. On November 21 he was started on placebo capsules, for which cortisone, 100 mg. daily,

was substituted four days later. Pre- and post-treatment strength tests are recorded in table 1. He showed improvement in these tests four days after starting cortisone and by December 2 his gait was nearly normal. The hormone was discontinued December 4. On December 9 the spinal fluid contained 39 mg. per cent of protein. Paresthesias returned in his feet and hands on December 12 and lasted four days. On December 18 strength tests showed no significant improvement over those obtained on December 9, and cortisone was again begun. No improvement was noted until December 23 when the patient regained the ability to do a deep knee bend and showed other improvement, as charted in table 1. By December 29 he was able to do several pushups and repeated knee bends. Further improvement was apparent by January 5 when cortisone was stopped. During the next six weeks he continued his course of slow, steady recovery. At the end of this time he could perform all assigned duties but his endurance was limited. He was returned to limited duty February 27, at which time neurologic examination was essentially normal except for absent deep tendon reflexes.

TABLE 1

FUNCTIONAL PERFORMANCE OF CASE 2 BEFORE, DURING, AND AT THE END OF CORTISONE TREATMENT.

Date	*Elevation of Leg 45° from supine position* (in seconds)		*Supporting Weight in Hand with arm 90° abducted* (in seconds) 3 *lbs.*		*Grip* (dynamometer in lbs.)		*Knee Bends*	*Pushups*
	R	*L*	*R*	*L*	*R*	*L*		
11/13/52	30	95	30	60	40	36	0	0
11/23/52	35	87	33	65	38	35	0	0
11/25/52 *Cortisone started*								
11/28/52	75	120	90	120	43	55	0	0
12/2/52	80	114	80	105	57	60	0	0
12/4/52 *Cortisone stopped*								
12/9/52	105	100	90	120	55	65	0	0
12/18/52	105	100	97	118	55	60	0	0
12/18/52 *Cortisone started*			(5 lbs.)					
12/23/52	112	170	88	86	65	65	2	0
12/29/52							5	2
1/5/53	160	210	110	125	78	80	10+	5

Case 3.—A 17 year old seaman had been well until December 4, 1952, when he had developed acute scarlet fever. He had been treated with penicillin, 300,000 units daily, for five days, followed by one similar injection one week later. The scarlet fever subsided uneventfully, but on December 21 he experienced general malaise, headache and anorexia. On December 27 he developed generalized urticaria which lasted three days. He then felt well until the third week of January 1953, when he suffered cramping pains in his legs. Gradually increasing weakness appeared during the next three weeks, first in the lower, then in the upper extremities. He noted pins and needles sensations in his hands and was unable to discriminate fine objects for approximately a week in mid-February. He lost 15 pounds in weight. During the first two weeks of February he shared in a mass anti-streptococcus program while at his duty station, receiving oral penicillin tablets. He was unable to recall having developed an aggravation of his symptoms during this time.

At the time of admission to the hospital on February 22, he was thin and generally weak but still ambulatory. Cranial neurologic function was intact. Diffuse, symmetrical

loss of muscle substance was noted in both upper and lower extremities, and weakness was elicited which progressed from moderate to marked as the examination moved distally over the extremities. Fine movements in his hands were seriously impaired, as were wrist movements. He had bilateral foot drop and had lost the ability to raise himself on his toes, but could raise his extremities against gravity at the trunk-extremity junctions. Sensation was intact to testing. Spinal fluid was normal, containing 41 mg. per cent of protein. Muscle biopsy from the left biceps and gastrocnemius muscles showed minimal atrophic changes.

No improvement in well-being or strength was detected for three weeks. He was placed on cortisone, 100 mg. daily, for eight days. Similar courses of cortisone were twice repeated with five day rest periods in between. There was no significant change in neurologic function during or after these courses of hormone, although his appetite increased and he had a sustained gain in weight of eight pounds coincident with the first course of cortisone.

DISCUSSION

Among other possible causes, an infectious virus has been postulated as responsible for acute polyneuropathies.[8] Since Shwartzman's[9] work has demonstrated enhancement of experimental poliomyelitis virus infections by cortisone, it was not given to the present patients until several weeks after their disease had reached a maximum. Also, the possible effects of cortisone could better be evaluated by selecting for treatment patients with fairly static clinical courses.

The improvement that followed institution and re-institution of cortisone in case 1 was so immediate and marked that coincidence was unlikely. In the two male patients polyneuropathy was associated with other manifestations of hypersensitivity to penicillin. One of these patients (who had a moderately elevated spinal fluid protein) had only a slow and gradual recovery while receiving cortisone; the other showed no response. Neither of these men suffered as severe or as proximal evidence of neural dysfunction as did case 1, neither had important sensory changes, and neither had particularly high spinal fluid proteins at the time of treatment. Both patients with Guillain-Barré syndrome previously reported as responding to ACTH or cortisone[1,2] had profound motor weakness, prominent defects in position and vibratory sensation, and significantly elevated spinal fluid protein levels. These signs may reflect nerve root edema with compression at root sheaths.[10,11] If nerve axons were not directly impaired, but were principally compressed, amelioration of root edema and decompression of the neuron might explain rapid improvement effected by cortisone. The patients with polyneuropathy who fail to respond to cortisone, on the other hand, may have suffered direct neuronal damage at either the root or a more peripheral level, precluding rapid functional restoration.

Previous examples of symmetrical polyneuropathy complicating penicillin herapy have not been found, though mononeuropathies and localized multiple neuropathies have been described. Broadbent, Odan and Woodhall's[12] patients developed mononeuropathy secondary to penicillin injections in and around nerve trunks. The same was true of Tarlov, Perlmutter and Berman's

case[13] and appeared to be true in two and possibly four of the seven patients reported by Kolb and Gray.[14] Two of the remaining three men described by Kolb and Gray had multiple neuropathy about the shoulder girdle similar to the type described by Burnard and Fox[15] and others[16,17] in military personnel following immunization or during recovery from diverse illnesses or traumata. Kolb and Gray's other case had a mononeuropathy, but this appeared so long after penicillin was discontinued that there seemed no likelihood of a direct traumatic lesion. In all the above patients, as well as in the ones reported here, nerve lesions following penicillin injections caused prolonged disability. These potential reactions, though rare, represent indications for the discriminate use, administration and supervision of penicillin therapy.

SUMMARY

Three patients with multiple symmetrical polyneuropathy have been treated with oral cortisone. One woman, who developed her illness 16 days postpartum and who had pronounced loss of motor and sensory functions with markedly elevated spinal fluid protein, had striking improvement while receiving the hormone. Two men suffered polyneuropathy apparently as a delayed sensitivity reaction to penicillin. One of these, who had a moderately elevated spinal fluid protein, experienced moderate slow improvement while receiving cortisone; the other had no change in his disability during the period of medication. Illness in these two men was prolonged, and represents an indication for discrimination in using penicillin therapy.

ADDENDUM

Since the present report was submitted, additional experiences using ACTH and cortisone in symmetrical polyneuropathy have been recorded. The author has observed an additional patient in whom ACTH induced no significant change. Eaton[18] states that of five patients at the Mayo Clinic with the Guillain-Barré syndrome four were treated with ACTH and one with cortisone. None showed any response. Merritt[19] has treated four additional polyneuritis patients with cortisone, and has observed nothing to indicate that cortisone has any effect on the disease. Newey and Lubin[20] and Blood, Locke, and Carabasi[21] have presented reports of single cases which improved while receiving ACTH. Recovery in the latter authors' patient was not prompt. Thus, improvement of polyneuropathy following corticotropin or cortisone therapy appears to be but an occasional and unpredictable phenomenon, possibly only of coincidental significance.

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The second indication in the treatment of megrim is to avoid or correct those external circumstances or internal conditions of the body which prove exciting causes of the paroxysms. I have already pointed out that where the malady is deeply rooted in the original constitution of the nervous system and the seizures observe an approximate regularity of recurrence with healthy intervals, they will too often continue to occur even when the most scrupulous care is taken to avoid whatever has seemed to provoke them. I also pointed out that a longer interval of freedom than usual is often followed by a more severe seizure, and I referred to the remarkable expression of one of my patients that "she knew she had a certain amount of suffering to go through, and would as soon have it regularly as not." It might seem therefore at first sight an unprofitable task to live in the constant observance of precautionary rules and an irksome self-restraint for so doubtful an advantage. There may be a certain amount of truth in this, (but it is no less certain that in the great majority of cases, even of the regular type to which I have referred, the malady is very liable to aggravation, and the seizures prone to acquire an additional facility of recurrence, from frequent exposure to the same exciting causes. Moreover in a great many instances the disorder is not of that well-developed and spontaneously recurrent type, and then by carefully avoiding certain well-known influences the patient may often enjoy long periods of exemption from his troublesome complaint. Hence we may say generally, that it becomes an important part of the treatment of megrim to discover what are the provocatives of the seizures in each individual case, and to take what measures we can for their prevention or removal.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Intracarotid and Intravertebral Metrazol in Petit Mal Epilepsy

*Foster E. Bennett, M.D.**

SINCE the demonstration that the three per second spike-and-wave complex seen in the electroencephalogram is almost pathognomonic of petit mal epilepsy,[1] many investigators have tried to discover its source. Because the petit mal pattern is bilaterally symmetrical in most cases a subcortical focus, possibly the thalamus, has been implicated.[2,3]

Metrazol (pentamethylenetetrazol) is closely bound to the petit mal pattern, and has been used extensively in animal experiments since it tends to induce repeated spikes and waves which simulate the petit mal complex. It is largely on the basis of these animal experiments that the thalamus has been considered to be the site of origin of petit mal discharges. In an effort to apply these observations to human patients with petit mal epilepsy, Spiegel and Wycis[4] undertook studies with the stereoencephalotome using electrodes placed in the human thalamus but their results are not convincing.

Clinically, Metrazol is frequently employed intravenously to precipitate seizures in epileptic patients, and those with petit mal epilepsy are exceedingly sensitive to the drug. Although this method of activation is very useful in establishing a diagnosis of epilepsy and in delineating foci of seizure activity, it fails to reveal the source of apparently generalized seizure discharges. The petit mal pattern appears to be one example of this type.

The blood supply to the brain is partitioned in such a manner that the internal carotid artery supplies the ipsilateral cerebral cortex, putamen, caudate nucleus, and preoptic area of hypothalamus. The thalamus is excluded from this circulation, but is irrigated by the thalamogeniculate and thalamoperforating arteries derived from the posterior cerebral and posterior communicating arteries. The thalamus depends on the integrity of the posterior cerebral artery, and when the latter becomes occluded, softening of the thalamus occurs.[5,6,7] Carotid arteriograms do not demonstrate the thalamic circulation,

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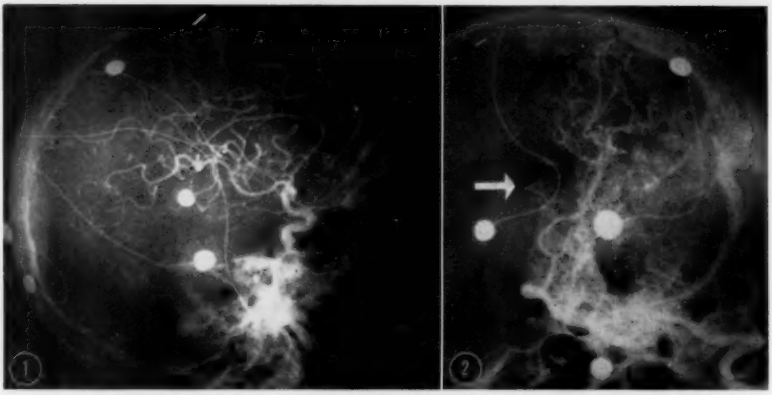


FIG. 1. A typical carotid arteriogram, showing the position of the scalp electrodes and a normal vascular pattern. FIG. 2. A typical vertebral arteriogram. The arrow points to the thalamogeniculate arteries supplying the thalamus.

but with proper timing the vascular supply of the thalamus can be seen easily by vertebral arteriograms.[8] This partitioning of blood supply would allow one to direct pharmacologic agents either to the cortical areas or to the central gray masses.

With these data in mind it was decided to study the effects of intracarotid and intravertebral injections of Metrazol during continuous electroencephalographic recording in patients suffering from clinical seizures of the petit mal type with three per second spike-and-wave discharges in their brain waves. Patients with petit mal variant epilepsy were excluded from this study.

METHOD AND MATERIALS

Patients were hospitalized for this study, and food was withheld on the day of the procedure. After premedication with 200 mg. of Seconal and 100 mg. of Demerol, they were taken to the electroencephalographic laboratory where scalp electrodes were applied in the standard positions.[9] Patients then were taken to the x-ray room, and after necessary arrangements for screening artifacts had been completed, continuous recording was started. Monopolar technic with interconnected ear electrodes was used in all cases, and recording was done with an eight channel ink-writing electroencephalograph.

Following the administration of intravenous Nembutal, intravenous Pentothal, or simply intracutaneous procaine, usually one of the common carotid arteries was punctured by percutaneous technic.[10] After the puncture had been secured, an arteriogram using 6 to 8 cc. of 40 per cent Diodrast was made to be sure that the injections of Metrazol would enter the internal rather than the external carotid circulation (figure 1). Then, starting with

5 mg. of Metrazol in 1 per cent solution, small amounts were injected rapidly (in one second) in successive increments until the petit mal seizure threshold had been reached. This threshold dose was injected repeatedly (every five minutes) to be sure that the Metrazol was causing the seizure discharges. Following this the other common carotid artery was punctured, and the same procedure was carried out. Finally, one of the vertebral arteries was punctured using a percutaneous technic, and the identical procedure was performed (figure 2). Occasionally, the vertebral puncture was made first, or after Metrazol injections had been completed in the first common carotid. Arteriograms were done with every puncture to visualize the circulation and to estimate the route of the Metrazol.

A total of nine patients were studied – four under Nembutal anesthesia, three under Pentothal anesthesia, and two under local anesthesia only. However, five of the patients who received barbiturates intravenously were awake at times during the procedures.

TABLE 1

EEG OBSERVATIONS OF NINE PATIENTS WITH PETIT MAL EPILEPSY SUBJECTED TO 17 COMMON CAROTID ARTERIAL PUNCTURES WITH INJECTIONS OF 1% METRAZOL

	No. of Punctures
Easily elicited classical petit mal pattern	13
Larval petit mal discharges	2
Repeated single spike-and-wave	1
No seizure discharge	1

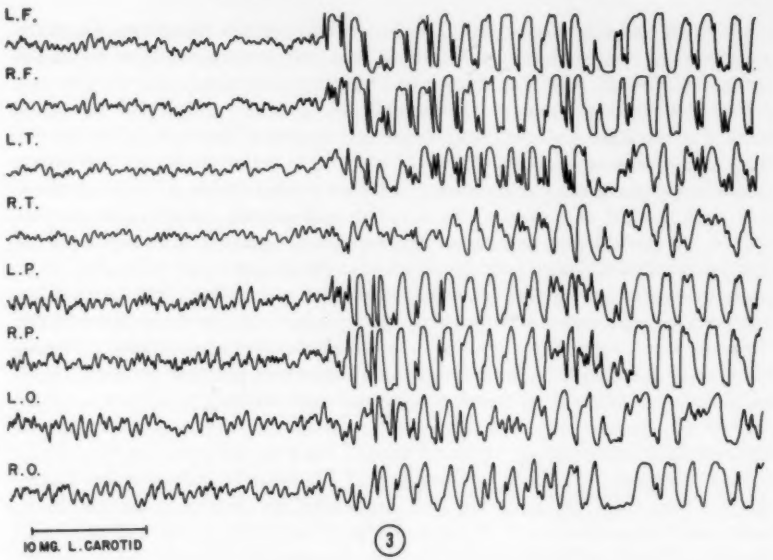
RESULTS

Seventeen carotid punctures were successful, and in 13 instances (table 1) the rapid unilateral injection of 5 to 15 mg. of Metrazol in 1 per cent solution consistently evoked within three to six seconds classical bilaterally symmetrical petit mal discharges lasting three to 40 seconds (figure 3). These discharges were accompanied by clinical petit mal seizures in all the conscious patients. In several instances patients probably were too deeply narcotized. For example, no petit mal discharges were obtained even with 50 mg. of Metrazol in one patient who had received too much intravenous Nembutal; whereas discharges had been evoked by the other carotid injections when the patient was awake. The latter common carotid artery was punctured again,

TABLE 2

EEG OBSERVATIONS OF EIGHT PATIENTS WITH PETIT MAL EPILEPSY SUBJECTED TO EIGHT VERTEBRAL ARTERIAL PUNCTURES WITH INJECTIONS OF 1% METRAZOL

	No. of Punctures
Easily elicited classical petit mal pattern	1
Short petit mal interrupted by grand mal discharges	2
Larval petit mal	1
Grand mal discharges	2
No seizure discharge	2



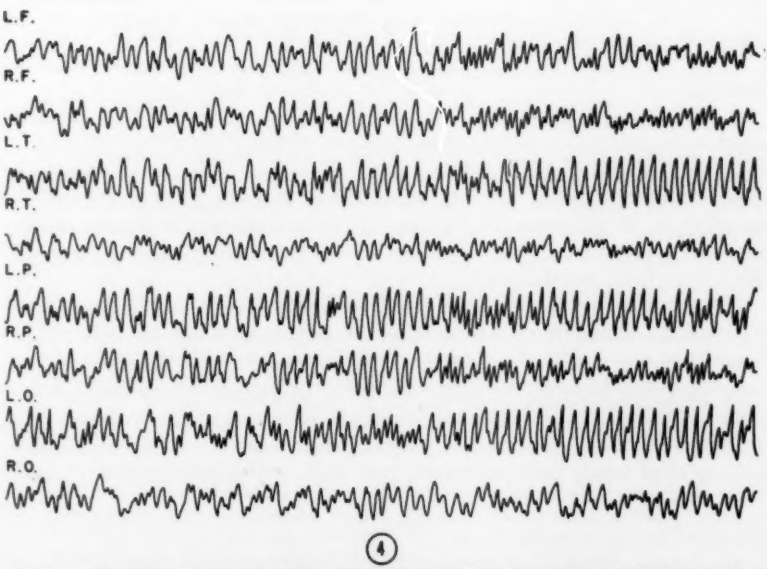


FIG. 3. Electroencephalogram of a fully conscious patient. Three seconds following injection of 10 mg. of 1 per cent Metrazol into the left common carotid artery the patient developed a classical clinical petit mal seizure. FIG. 4. Electroencephalogram of a patient under light Pentothal anesthesia. Eight seconds following injection of 35 mg. of 1 per cent Metrazol into the vertebral artery the patient developed spiking, maximal in the left temporo-parieto-occipital leads. During this period he ceased breathing for 40 seconds. No clonic movements were observed.

but no petit mal discharges could be elicited by Metrazol injections. On three occasions the petit mal seizure threshold was deliberately exceeded by larger doses of Metrazol. After a short run of three per second spike-and-waves, diffuse spiking supervened. Thereupon, the patients developed adversive turning of the head and eyes, and clonic movements of the extremities contralateral to the side of injection; a generalized seizure followed shortly thereafter.

Eight vertebral arterial punctures were successful (table 2), and of these, only one showed the same classical petit mal pattern comparable to that evoked by intracarotid injections of Metrazol. Intravertebral injections of Metrazol tended to cause spiking (figure 4). When petit mal discharges were present, usually they were associated with multiple spikes, and in most instances the spike-and-wave complex was poorly formed. In general, more Metrazol was required to produce seizure discharges of any kind. In two cases no seizure activity could be evoked, but these patients probably were too deeply narcotized. Although long grand mal discharges were frequently elicited, no clonic movements were ever observed. In two conscious patients intervertebral injections of Metrazol caused flushing followed by blanching, profuse diaphoresis, nausea, vomiting, and bradycardia followed by tachycardia. This train of symptoms was succeeded by flattening of the brain waves and disappearance of spontaneous petit mal activity, so that petit mal discharges could no longer be elicited by intracarotid injections of Metrazol. One patient, lightly anesthetized with Pentothal, ceased breathing for 40 seconds during a long period of spiking (figure 2).

DISCUSSION

The similar partitioning of cerebral blood supply by the carotid and vertebral arteries in cats was utilized by Shimizu, Refsum, and Gibbs[11] to obtain differential concentrations of Metrazol in the cortex and in the thalamus. These authors disagreed with the observations and conclusions of previous investigators. They concluded that in cats spike-and-wave discharges of the petit mal type induced with Metrazol are more readily obtained from the cortex than from the thalamus.

Clinical evidence does not completely confirm the theory of thalamic origin of petit mal epilepsy, but tends to indicate that the cortex may be responsible. Tumors residing within the third ventricle and invading the thalamus do not cause petit mal seizures, but are more likely to produce diencephalic autonomic epilepsy.[12] Vascular lesions leading to infarction of the thalamus also fail to initiate petit mal seizures. On the other hand, in a small percentage of cases head injury may precipitate petit mal, and pneumoencephalograms often demonstrate cortical atrophy in these patients.

SUMMARY AND CONCLUSIONS

Nine patients with petit mal epilepsy were subjected to 17 common carotid and eight vertebral arterial punctures. Small amounts of Metrazol in 1 per cent solution were injected rapidly into these vessels. Unilateral intracarotid

injections produced bilaterally symmetrical petit mal activity which was elicited time after time. A unilateral focus of seizure activity never was seen, nor was the three per second spike-and-wave more well developed on the ipsilateral side. This was expected, for interhemispheric spread of electrical activity is so rapid and complete that focal discharges may appear to be generalized when an ink-writing apparatus is used. The spontaneous appearance of the petit mal pattern in every lead of the electroencephalogram is not necessarily a sign of subcortical origin.

From the data obtained the following conclusions may be drawn:

1. In a series of patients with petit mal epilepsy studied under comparable conditions, petit mal seizure discharges could be elicited easily by unilateral intracarotid injections of Metrazol, but only occasionally and incompletely by intravertebral injections of the drug.

2. These studies support the thesis that the thalamus is not the site of origin of petit mal seizures, and that the cerebral cortex still cannot be excluded as the possible source.

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The conclusion, then, is that the convulsions in idiopathic epilepsy may propably be due to the discharge of any of the gray matter of the encephalon, which subserves sensori-motor processes. This brings us, however, to the second question: Is the seat of the primary discharge the seat of the disease? If by such discharge, all the symptoms can be accounted for, we have no need to go further, and the theory that any other pathological process underlies the phenomena must rest upon its independent evidence. To learn, therefore, whether the seat of the discharge can be regarded as the disease, we must consider, first, whether there are any symptoms for which the discharge of gray matter, which causes the aura and the convulsion, cannot account; and, secondly, whether there is direct evidence of any other pathological process.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases* published in 1885.

Epileptic Disorders in the Aged

Philip T. White, M.D., Allan A. Bailey, M.D.
and Reginald G. Bickford, M.B.

In these days of increased longevity the neurologist is more frequently confronted with the problem of epileptic disorders in the aged. As a means of stimulating awareness of and interest in this problem a clinical and electroencephalographic study of 107 patients who experienced onset of seizures after the age of 50 years was undertaken. The subsequent course of 72 of these patients was studied through information obtained from a follow-up questionnaire or from other sources.

Gowers[1] in 1881 was one of the earliest to write about the occurrence, incidence and sex distribution of epilepsy in elderly people. This study confirmed the earlier impressions that a preponderance of males are afflicted and that a small percentage of patients have a positive family history. We found a somewhat greater incidence than did Gowers: our estimate being 4 per cent, or 107 patients out of an estimated 2,700 cases of seizures in patients of all ages, seen in a three year period in the electroencephalographic laboratory. Sympson[2] and Talbot[3] have also commented on the small percentage of such patients. Two of our patients may have had seizures as children but had subsequently been free of seizures for more than 40 years. Such data may be of academic interest, but the physician is more keenly concerned with finding the underlying cause of the seizures and with the ultimate outcome of the individual patient.

Figure 1 depicts the various diagnoses and their incidence in the 107 patients studied. Diagnoses were accepted and recorded as made by the clinicians who examined the patients. As can be seen, the commonest diagnosis made was that of generalized cerebrovascular disease, with an incidence of 32 per cent. Of this group, 90 per cent had hypertension or sclerosis of vessels in areas of the body where it could be identified, which might be accepted as presumptive evidence of vascular changes in the brain in this age group. There was evidence of focal brain damage, presumably on a vascular basis, in 8 per cent, and hypertension alone in 6 per cent. It should be em-

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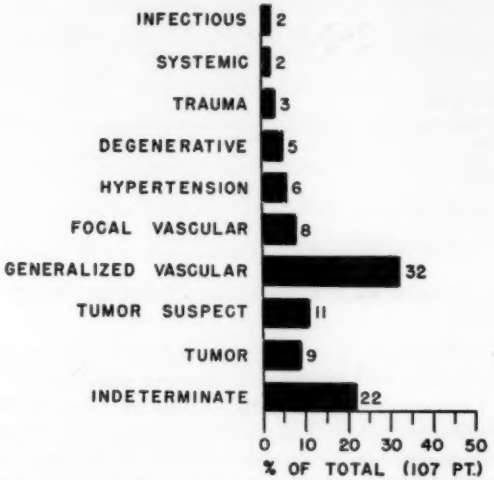


FIG. 1. Relative frequency of the clinical diagnoses underlying epileptic disorders with onset after 50 years of age.

phasized that these diagnoses were determined clinically, but if they are accepted as valid, such factors are noted to be five times as frequent as a cause as are intracranial neoplasms, which were diagnosed in 9 per cent of the patients. Of the patients with tumors, four were known to have a metastatic variety. While an additional 11 per cent of the patients were diagnosed as being tumor suspects, it sometimes seemed that such a diagnosis was made simply because of the history of seizures. Other clinicians preferred to classify the cause as indeterminate pending clarification during observation. We were able to determine the subsequent course of 28 of the patients in the two groups last mentioned, one of whom had died of metastases to the brain and two of whom were worse. The remainder were either unchanged or had improved.

Out of a total of 65 patients who returned the follow-up questionnaire, only three complained that their seizures were worse and five indicated that further neurologic signs had developed. This is in contrast to the 38 patients who stated they were improved and the 19 who indicated no change. The response of patients to anticonvulsants was difficult to evaluate, but it was the general impression that these patients responded favorably. In some cases it was apparent that improvement had occurred in the absence of continued use of the medication.

Of the 107 patients in this group, 20 are known to be dead. Three of the 20 deaths were due to intracranial neoplasms and three other deaths were probably due to disease of the nervous system. In the other patients death

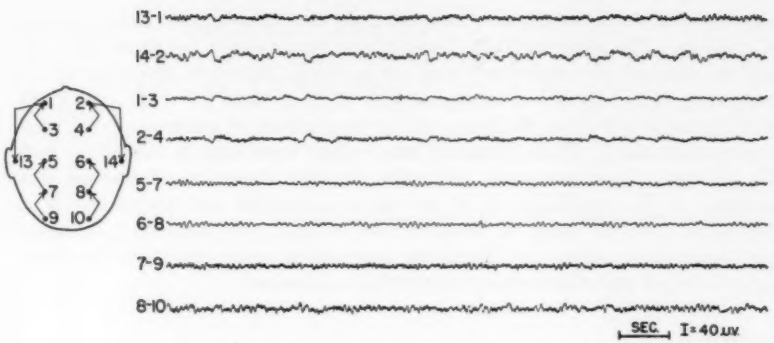
TABLE 1
KNOWN DURATION OF LIFE AFTER ONSET OF SEIZURES

Duration, years	*Patients, last reported*	
	Living	*Dead*
1 or less	0	8
2 to 5	32	9
6 to 10	13	3
More than 10	7	0
Total	52	20
Average duration, years	6	2.7

was due to neoplasms outside the nervous system in four, to cardiovascular-renal disease in seven, and causes unknown but probably not neurologic in three. Table 1 summarizes the duration of life of those known to be dead and the known duration, at the last report, in those living. It does not appear that seizures in themselves necessarily shorten the normal life expectancy, since the causes of death were not markedly different from the commonest causes of death listed for this country.[4]

No indication as to the prognosis could be derived from the type and frequency of occurrence of the seizures. Patients with focal seizures constituted 18 per cent of the group, while 44 per cent had generalized seizures and 38 per cent had the two combined. In the 27 patients who either died, became worse or developed further neurologic signs, an almost identical distribution of the types of seizures was seen. The focal seizures encountered were predominantly of temporal lobe origin, with an incidence of 43 per cent in these older patients. Lennox[5] has indicated an incidence of 20.7 per cent in 1,900 patients of all ages. We encountered no patients with petit mal, although one may have had such prior to the age of 20 years.

Because the electroencephalogram had been helpful in understanding the general problem of epilepsy, its usefulness in the group of patients under discussion was evaluated. In studying these records it was quickly apparent that there had been a shift toward the abnormal, with normal records in only 20 per cent compared to a control group in which 85 per cent of the records were normal. This shift was even more obvious in the records of the 27 patients with the worst clinical course. Fifty-two per cent of these had markedly abnormal records, suggesting focal disturbances. Figure 2 illustrates such a record with random slow waves overlying the disturbed area. When the electroencephalogram was suggestive of a destructive lesion, as it was in 17 of the 107 patients, the clinical diagnosis proved to be correspondingly grave in 77 per cent of this small group. Figure 3 represents an example of an additional 15 per cent of the records which were abnormal but nonlocalizing, so that a total of two-thirds of these 27 patients had definitely abnormal records.



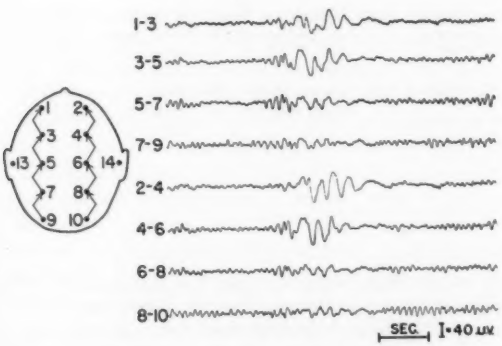


FIG. 2 (*above*) Random, irregular, slow waves arising from the right temporo-occipital area in a patient with a tumor of the right temporal lobe.

FIG. 3 (*left*) An example of the non-localizing but definitely abnormal rhythmic discharges seen in some patients of this study.

Of the ten patients with definitely diagnosed tumors, eight had abnormal records of a focal variety, seven of which are known to correspond to the site of the lesion. One of the cases was diagnosed as diffuse metastatic disease and this was associated with evidence of diffuse disturbance in the electroencephalogram, while in another patient with a meningioma of the falx cerebri the record was of the type often associated with projected disturbances from midline lesions. Thus while not infallible, electroencephalography had some prognostic value. It is sufficiently easy to perform that it should not be overlooked in assessing epileptic disorders in the aged.

SUMMARY

A group of 107 patients with the onset of seizures late in life are reviewed. The diagnostic and prognostic aspects of these patients have been examined from a clinical and electroencephalographic viewpoint. Cerebrovascular disease of some type was presumed to be the cause of seizures in the majority of instances, and the follow-up study supported the concept that tumors were present in only a small group. Although statistics are of little practical value in evaluating any individual patient, this study would suggest

that in the absence of definite evidence of an intracranial tumor, such a cause is unlikely. The prognosis was favorable in the majority of these patients, and the over-all life expectancy was not markedly reduced. The duration of symptoms varied from less than one year to more than 20 years, and there was a great variation in the frequency of occurrence of seizures. Focal seizures predominantly of the temporal lobe variety were seen in more than half the patients. There was some indication that the electroencephalogram was of value in the establishment of the proper diagnosis and prognosis. It is concluded that the onset of seizures late in life is not necessarily a cause for undertaking exhaustive diagnostic procedures as a substitute for competent clinical and electroencephalographic evaluation.

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The attacks or seizures which characterize epilepsy are commonly divided into two classes, major or severe, and minor or slight. These two forms, although clearly distinguished in their general characters, are not separated by a sharp demarcation. In the major attacks (*grand mal*) there is loss of consciousness often prolonged, and severe muscular spasm. In the minor attacks (*petit mal*) there is commonly brief loss of consciousness without muscular spasm; sometimes there is loss of consciousness and slight muscular spasm; very rarely there is slight muscular spasm without loss of consciousness.

In severe attacks, the patient, if standing, falls to the ground; in slight attacks he may or may not fall. Hence the term "epilepsy," equivalent in meaning to the old English name, "falling sickness," is founded on a feature which is not invariable.

In very severe attacks, muscular spasm comes on at the same time as consciousness is lost. In less severe fits, the muscular spasm may commence before consciousness is lost, and the patient is then aware of the onset of the fit. Still more frequently the spasm and loss of consciousness are preceded by some sensation. The sensation, or commencing spasm, which informs the patient of the oncoming attack, constitutes the "warning" or "aura" of the fit.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Is the Order of Birth a Factor in Epilepsy?

Joseph K. Orr, M.D. and Frank Risch, Ph.D.

It now seems generally accepted that epilepsy is not a disease but a symptom of disturbed brain function. It is also agreed that the factors which underlie the disturbance of function and produce convulsive seizures are both numerous and variable, probably different in every case. Recently, considerable emphasis has been put on organic disease of the brain as a factor in epilepsy, and in this connection so-called "birth trauma" and "cerebral anoxia" are of interest. Then again in those cases where no specific pathology has been demonstrated, as is true in so many cases of epilepsy, the genetic influence has been stressed. With a multiplicity of possible causes, the recent report by Nielsen and Butler[1] is of particular interest because the significant factor in a number of cases of idiopathic epilepsy is thought by them to be "birth primacy." In another recent survey by Ahlstrom,[2] however, similar findings have not been corroborated. Recognizing the existing disparity of these reports, any data which may shed further light on the relationship of epilepsy and birth order are, therefore, of interest and importance.

PROCEDURE

In 1950 the department of medicine and surgery of the Veterans Administration appointed an epilepsy committee of prominent neurologists in the Los Angeles area to study the problem of epilepsy in veterans, to collect data, and to recommend ways and means of rehabilitating these individuals. A standard routine interview form amenable to statistical treatment was developed to obtain a detailed array of information about the veteran. This form included several questions relating to the patient's sibling relationship, mainly:

1. How many children living and deceased were there in your family?
2. What position of birth do you hold?
3. Have any other members of your family ever had epilepsy?

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Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 9, 1953.

Unfortunately these questions were only incidental to the over-all investigation and were included principally as routine anamnestic items. It was some time during the course of gathering data that the possible relationship between size of family, birth order and epilepsy was first recognized. Had the items been structured specifically to determine the importance of birth order, the limitations of this study as listed in a subsequent section would not have occurred. However, the collected information seems worthy of reporting inasmuch as it may further the cause for a much needed clarification of birth order and epilepsy.

RESULTS

Findings are based on the responses given by 158 veterans, of whom 88 were institutionalized in the Veterans Administration domiciliary and 70.were non-institutionalized living in the Los Angeles area. All patients were males who had served in the armed forces, and all had been diagnosed as having epilepsy of idiopathic type, although in a few the question of a complicated secondary head injury existed. The average age at onset of seizures was 34 years. The average number of children per family was 5.6. In the 158 families the average birth position of the epileptic veteran was found to be near the fourth born (3.9) rather than near the third born (2.8). The latter value (2.8) reflects a position determined by chance factors alone wherein the average number of children per family is found to be 5.6. Inspection of figure 1 reveals that the over-all difference between the obtained and expected mean order of birth (3.9 – 2.8) is an accumulation of differences between obtained and expected birth order for each family size. With families ranging in size from one to 14 children, it can be noted that in 11 out of 14 different size families the obtained mean order of birth was greater than the expected one. Furthermore, among 158 families there were 24 families having 10 to 14 children, and 10 families having only a single child. Generally, it was found that the larger the family the more likely was it for the epileptic to be the youngest or near youngest.

DISCUSSION

In discussing the possible significance of these statistics and the reasons they are at variance with those obtained by Nielsen and Butler[1] and by Alstrom,[2] it might be pointed out that Nielsen and Butler reported on 780 subjects taken from a large group of epileptics numbering 3,275 in a home for the feeble-minded. Of the 780 patients, 279 or 35.8 per cent, were found to be first born. This apparently included subjects who were only children. The authors obtained a ratio of 1.79 first born to each subsequent born, a ratio they felt to be significant. Alstrom on the other hand found 304 first born out of a group of 870 epileptics, but notes that 105 of this number were from families with only one child. Excluding only children altogether leaves

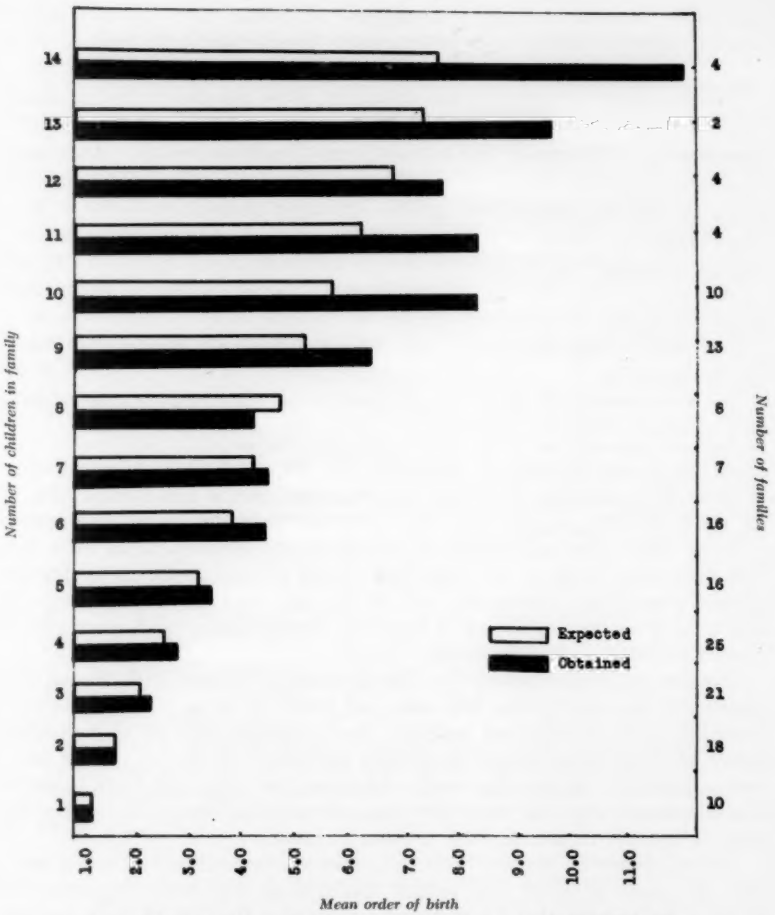

FIG. 1. Relationship between family size, order of birth and the individual with epilepsy.

199 first born as against 192 last born, an insignificant difference. Table 1 presents a more detailed comparison of statistical values as derived from the three separate studies.

This report would seem to argue again for caution in dealing with statistics and to indicate the traps everywhere present. It seems evident that the type of population used and the selectivity of the sampling are all-important variables and may account for the variations in the reports mentioned. Alstrom, who surveyed a cross-section of epileptics of both sexes and all ages

TABLE 1
COMPARISON OF CERTAIN CHARACTERISTICS OF EPILEPSY IN THREE POPULATION SAMPLINGS

Characteristics	NIELSEN & BUTLER	ALSTROM	AUTHORS
Type of patients with epilepsy	*Defective children, male and female*	*Children and adults, male and female*	*Adult male*
Number of patients	780	897	158
Average number of children per family	4.2	4.4	5.6
Number of patients First born—including only born	279—(35.8%)	304—(33.9%)	23—(20.2%)
Number of patients First born—excluding only born	not given	199—(22.9%)	22—(14.0%)
Number of patients Last born—excluding only born	not given	192—(21.0%)	45—(28.5%)

from the general population, concluded that his results do not provide support for the assumption that "delivery traumata" play a considerable role as an etiologic factor in epilepsy. However, one must not forget that certain patients might quite conceivably be admitted to institutions at an early age, and may never come to the neurologic clinics or neurologist caring for the general population. Perhaps the bulk of the cases used in Nielsen's study did not come from the population at large but, being handicapped, were placed in an institution quite early in life.

Nielsen and Butler believe that "the incidence of known birth trauma was essentially the same in the first born and others in their series." However, regarding birth injuries and epilepsy, Ford[3] reported that no characteristic lesion has been demonstrated in epilepsy and that birth injuries are not common. Courville[4] agrees with Ford's statement, but adds that birth injury is a much abused term. He feels that neonatal anoxia as distinguished from the true mechanical trauma at birth is more common.

The idea that the order of birth bears a significant relationship to the etiology of certain physical and mental disturbances has been suggested by Benda.[5] He believes that the maternal condition at the time of birth and the mother's endocrine status is a definite etiologic agent in mongolism. Whether this might also be true in some epileptics remains to be seen, but it is suggestive.

LIMITATIONS

Several limitations concerning our data should be considered. First, the patients used in the study were a select group made up of male veterans. Second, several cases of seizures following trauma are known to have been included. Third, the reliability of reporting siblings dead and living might be questioned, although every attempt was made to obtain accurate figures.

Fourth, the age of the mother at patient's birth was not obtained. Fifth, the exact number of siblings having epilepsy was not verified, although all patients denied any family history of epilepsy. Lastly, the question of birth trauma in the patients was not investigated.

SUMMARY

This is a report on 158 epileptic veterans, both institutionalized and non-institutionalized.

1. Routine questioning regarding sibling relationship revealed a strong indication that epilepsy occurred more frequently in people approaching the end of the line of birth rather than in those holding the position of first born, as indicated by other studies.

2. Generally it was found that the larger the family the more likely was it for the epileptic individual to hold the youngest or near youngest birth position.

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The subjects of epilepsy sometimes, but rarely present sudden paroxysmal outbursts of mental derangement, often with violence, and a tendency to injure others. The maniacal attack is usually brief, often lasting for a few minutes only, sometimes for an hour or two. It was formerly thought that such outbursts represented and constituted an attack of epilepsy. In the majority of cases, however, it is certain that, as Hughlings Jackson maintains, the mental derangement is the sequel to a fit, and is really a form of the automatic action which may succeed an attack, sometimes severe, much more commonly slight.

If the preceding minor attack is very slight, it may readily be overlooked, and hence the psychical disturbance be regarded as primary. Whether this is true of all instances of maniacal outbursts in connection with epilepsy is doubtful. In rare cases (as Esquirol and other good observers have pointed out) an act of violence precedes a fit. We have seen, in the account of modes of onset, that the aura of an attack may sometimes consist in a complex or coordinated mental process, or a visual idea. There is nothing inconsistent with ascertained facts in a sudden act of violence as the result of the initial discharge.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Clinical Use of Piromen in Spinal Cord Diseases and Injury

Walter J. Friedlander, M.D. and Pearce Bailey, M.D.

It is apparently fairly well accepted that following injury to the central nervous system there is: (1) some attempt on the part of the nervous elements to regenerate, although it is doubted whether this is a very vigorous attempt,[1–7] and (2) a considerable glial reaction which appears within a few days that may act as a barrier through which the new fibers cannot pierce.

In 1949 Windle and his associates,[8] while investigating the site of action of a new pyrogenic polysaccharide, Piromen,* found histologic evidence of regeneration of a transected spinal cord. Their subsequent[15–20] work in cats and dogs treated with Piromen demonstrated: (1) some anatomic regeneration of the cord, provided the separation between ends was no greater than 1 mm., with the new fibers aligned along a loose reticulum much like that seen in a regenerating peripheral nerve; (2) the absence of any massive gliosis; and (3) good vascularization. The sooner after injury the drug was begun, the longer it was continued, and the younger the animal, the more evidence there was of anatomic regeneration. It is important to note that these workers have not reported definite functional return after transection in treated animals; however, electrophysiologic studies on chronically treated preparations have shown conduction of electrical impulses immediately beyond the glial scar though in a less than normal quantity. Also, animals treated for up to eight months have shown increasing muscular tone and

*Piromen[9] is a complex bacterial polysaccharide obtained from the bacteria Pseudomonas by tryptic digestion. It is a constant cellular anabolite, not destroyed by autoclaving or passing through a Berkefeld filter.[10] A typical list of constituents is: 26.8 per cent desoxyribonucleic acid, 8.1 per cent ribonucleic acid, 7.0 per cent hexosamine, negligible amount of protein, no lipid, 12.9 per cent ash, and 45.2 per cent unidentified. The hexosamine is one of the pyrogenic substances; there are probably others in the unidentified portion. The drug is only slightly antigenic.[11] The fever that is produced originates in the central nervous system;[8,12] it is mediated by the autonomic nervous system;[13] and it can be blocked by the usual antipyretics.[14]

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Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 9, 1953.

TABLE 1
VARIOUS DIAGNOSES AND GENERAL IMPRESSIONS OF CLINICAL RESULTS (GROUP A)

Diagnosis	*Total No. of patients*	*No effect*	*Questionable effect*	*Probably some beneficial effect*
Traumatic myelopathy	66	46	15	5
Multiple sclerosis	6	1	0	5*
Tumor	4	3	1	0
Herniated intervertebral disk	2	1	1	0
"Degenerative disease of the cord"	2	1	0	1
Arachnoiditis	2	0	2	0
"Transverse myelitis"	1	1	0	0
Myelopathy following cyclopropane anesthesia for diaphragmatic hernia	1	1	0	0
Postoperative myelopathy for herniated cervical disk	1	1	0	0
"Thrombosis following dorsolumbar sympathectomy"	1	1	0	0
"Thrombosis, non-traumatic"	1	0	1	0
Tabes dorsalis	1	0	1	0
"Paraplegia due to Bang's disease"	1	0	1	0
No definite diagnosis given	29	28	1	0
TOTAL	118	84	23	11

*All 5 of these patients were reported by the same physician.

function,[21] though as of now it is not definitely known whether this is reflex or not. Freeman,[22] working independently, reported seeing clinical improvement in cord-transected animals several months after Piromen treatment was begun.

In spite of this encouraging experimental work, the only report on the clinical efficacy of Piromen indicates that the drug is probably of little value in treatment of neurologic patients.[23] In order to investigate further the clinical value of this drug the following survey was conducted.

RESULTS

A survey of the clinical results in 118 patients with spinal cord disease and injury (group A), cared for by 55 different physicians, was obtained. Many of the patients were not given complete neurologic examinations. The general, sometimes vague, impression gained by the physicians was that only about 10 per cent of the patients may have obtained some objective benefit. The various diagnoses together with the general impressions of the physicians are shown in table 1.

The protocols on 64 patients (group B) out of the entire series were accompanied by sufficient data to allow us to arrive at a more definite impression. Of these, only 8 per cent may have benefited by the drug. The findings are

TABLE 2
CLINICAL RESULTS IN GROUP B

Total number of patients	*No effect*		*Questionable effect*		*Probably some beneficial effect*	
	Number of patients	*Per cent*	*Number of patients*	*Per cent*	*Number of patients*	*Per cent*
64	44	69	15	23	5	8

summarized in table 2. The amount of each dose, the schedule of dosage, and the route of administration of the drug varied so much that it was impossible to arrive at any conclusions in regard to these particular factors. However, in 41 patients (group C) there was sufficient information to compare the clinical results, the length of total treatment, and the length of time that elapsed between the injury or onset of symptoms and the beginning of therapy. These results are summarized in table 3.

TABLE 3
CLINICAL RESULTS IN GROUP C

	Time Piromen begun after injury	*No effect*	*Questionable effect*	*Probably some beneficial effect*
Treated for one month or less	Less than 1 week	2		
	1 week to less than 1 month	2		
	1 month to 6 months	4		
	Over 6 months	1	1	
Treated for more than 1 month	Less than 1 week	1	2	
	1 week to less than 1 month	3	1	
	1 month to 6 months	4	2	2
	Over 6 months	8	5	3
Total number of patients		41	25	11	5

The five patients in group B who showed some improvement which could possibly be attributed to Piromen were given the drug for over one month, and, interestingly, all of them had their disability for periods ranging from two to 15 months. Only one of these patients may have had a complete cord transection; however, what improvement there was in this particular patient was only in the most proximal segments and this may have actually represented only recovery from spinal shock and/or decrease in edema about the site of injury.

The following case is an example of a rather common response to this drug:

A 50 year old physician was given a spinal anesthesia for an exploratory laparotomy four years ago. About one year later he noted that he was dragging his left leg, he experienced easy fatigability of both lower extremities, and he had difficulty knowing where his feet were, particularly in the dark. Twenty months after the initial surgery, neurologic

examination revealed an absence of vibratory sense up to and including the crests of the ilium, complete loss of position sense in the feet, and a decrease in pain and touch up to the level of about D-8. A laminectomy revealed an arachnoiditis. Following surgery and up until the present time, there has been a gradual and slight improvement, the course of which has not been influenced by any medication. When the patient was examined recently he could barely perceive vibration up to the crests of the ilium, he could not correctly localize small movements of his toes though he could accurately perceive gross movements, and though there was still a pain and touch level at D-8, these modalities were only slightly impaired. He had received Piromen subcutaneously for a period of three months beginning two years and nine months after the original spinal anesthesia and eight months after the laminectomy. The schedule of dosage was about 5 microgm. a day for a month, followed by a rest period of two weeks; higher doses produced generalized aching and a low grade fever.

Many of the patients experienced a very definite sense of well being, starting shortly after treatment was initiated.

There were two deaths in this series; one patient died because of his cord injury and the other died of a coronary occlusion several weeks after his spinal injury. In both cases it seems unlikely that Piromen played any role in their demise. One patient in this series, after the tenth intravenous injection, which represented a two-gamma increase in dosage, immediately developed flushing, dyspnea, imperceptible pulse, and pallor followed by cyanosis, but within one hour, he was again normal, and future injections did not produce such a severe reaction. Headache, malaise, cramps in the extremities, abdominal cramps, nausea and anorexia were not infrequently reported shortly after an injection.

The experience of others with this drug's toxicity might be commented upon here. In the rabbit, large doses have not produced any significant changes in the liver, kidney, intestine or brain.[24] One death has been reported following its use in a patient with asthma where the drug was used for treatment of that condition,[25] the clinical picture resembled anaphylactic shock. Exacerbation of a mild rheumatoid arthritis during Piromen treatment for a neurologic disease has been reported by Bailey;[23] when treatment was stopped, the arthritis receded only to recur when Piromen was again started.

DISCUSSION

The blood cell response of the body to Piromen injection suggested, at one time, that its action was akin to that of cortisone or ACTH. However, as further studies were conducted it became apparent that there were several striking and important differences between them. These have been summarized in table 4. It can now be speculated that Piromen, by causing a febrile response, will produce a stressful situation and, hence, some of the bodily changes that are found are probably due to ACTH or cortisone. However, this particular pyrogen produces other changes too, and it is reasonable to assume that these additional changes are those which either independently or in combination with ACTH or cortisone are responsible for whatever effects Piromen has in repair of nervous tissue. The question should be raised whether

TABLE 4

	ACTH	*Cortisone*	*Piromen*
Astrocytic proliferation after central nervous system injury	Slight inhibition	No effect	Marked inhibition
Circulatory eosinophiles and neutrophiles after adrenalectomy[26]	No change		Decrease
Anaphylactic reaction	Decrease[27,28]		Increase[28,29]
Thymus, lymph nodes	Atrophy[27]		Hyperplasia[18]
Wound healing	Impaired[30–32]		Improved[33,34]
Pyrogenicity	Antipyrogenic?[35]		Pyrogenic

whatever beneficial effects are due to Piromen may not also be produced by any other pyrogens and/or bacterial polysaccharides.

The fact that the five patients who may have benefited from Piromen had their injury or disease for over two months before therapy was begun suggests that the action of this drug is not merely to retard the rapidly-forming glial barrier and thus allow nerve fiber regeneration. Added to this discrepancy between theory and reported clinical results is our impression that what neurologic improvement was noted often occurred almost too rapidly to be explained simply by the regeneration of nerve fibers. It would seem more reasonable that there may be improvement of an only partially destroyed function rather than a total regeneration of a spinal tract. The feeling of a sense of well being similar to that which often accompanies ACTH or cortisone may contribute significantly to the patient's improvement by increasing his desire to get well, his activity, and cooperation in physical therapy, and so on.

Many of the patients in this series undoubtedly received an inadequate amount of Piromen for a too short period of time. If this drug has any specific central nervous system effect, it should reach the central nervous system directly. Clinical evidence that this does occur is the presence of fever since this is a known action of Piromen. The febrile dose varies considerably from individual to individual but is fairly uniform in a particular person; the febrile dose in humans may be as low as a fraction of a gamma or as high as 400 gamma. Hence, no set schedule can be given for all patients. Windle[21] suggests an initial dose of 5 gamma intravenously, increasing gradually until a febrile response is obtained. On the other hand, if a severe response is obtained with the initial treatment, dosage should be reduced. One objection to starting with a very small dose is that a tolerance may develop before a febrile response is obtained. The febrile-producing intramuscular dose is roughly five to ten times larger than the intravenous dose. Since the body will develop tolerance to a febrile dose, a rest period of a week or two every two weeks will prevent the necessity of gradually increasing the amount over the long period that the drug should be administered. If this series can at

least be used as a guide of what not to do, any course of treatment of less than two months is probably useless.

SUMMARY

This is a survey of 118 patients with spinal cord injury or disease who received Piromen; only about 10 per cent may have had some beneficial results. We are unable to arrive at any definite conclusions as to the usefulness or uselessness of this drug in these neurologic conditions, principally because the dosage and duration of treatment was inadequate in many patients. However, the results, though certainly not very encouraging, are such as to suggest that further clinical trial of Piromen is warranted, provided a more realistic schedule of dosage is pursued.

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The second form of psychical disorder which sometimes attends the development of megrim is Affective or Emotional. It is not uncommon for the attack to be preceded or ushered in by symptoms of this kind. Remberg mentions irritability of temper as premonitory. Tissot records the case of a medical man who was an habitual sufferer from true migraine; he enjoyed excellent health between the paroxysms, but always became depressed and ill-humoured a day or two before. In other instances great mental depression forms a part of the paroxysm itself. Dr. Dwight, writing, I have little doubt, from his own experience of sick-headache, says: "From the first perception of uneasiness in the stomach the spirits begin to flag. They grow more and more depressed until cheerful thoughts and feelings fly away, and the patient conceives himself the most wretched of human beings and feels as if he were never to be otherwise. What, perhaps, is a litle singular is that the intellect, during the severity of the pain, is peculiarly clear, precise, and capable of making the most minute distinctions upon intricate subjects. And these operations of the mind, though very painful, are wholly beyond control; nor in these moments of depression – though reason suggests the folly of despair and the fallacy of the belief which it inspires – will the feelings assent to its suggestions." My patient A. M., who likewise suffered from the sick form of the malady, characterized her mental condition at this period as one of "reckless" despondency.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Therapy of Myasthenia Gravis

Paut F. A. Hoefer, M.D., Henry Aranow, Jr., M.D. and Lewis P. Rowland, M.D.

Myasthenia gravis is characterized by weakness and excessive fatigue of striated muscles without anatomic changes in the nervous system or in the muscle proper except for occasional lymphorrhagias. While any of the muscles may be affected by the myasthenic process, there is a predilection for certain muscle groups, particularly those innervated by cranial nerves. Weakness of extraocular muscles with diplopia and ptosis, facial weakness and weakness of mastication and deglutition, dysarthria and, most important, dyspnea are found at one time or another in most of the typical cases.

The course of the disease is quite unpredictable. The onset is often insidious but sometimes it may be fulminating. The distribution of weakness varies a great deal from time to time in any given patient, as does the response to therapeutic measures. Spontaneous remissions occur in a fairly high percentage of cases. Sudden exacerbations, especially in association with upper respiratory infections but also at the height of apparent recovery, may precipitate a fatal crisis.

In some cases, adequate restitution of muscle strength may occur with rest alone, but in most instances drug therapy is needed. Failure of the vital functions of swallowing and breathing require special measures. In view of the variations in the course of the disease, flexible long-range planning of treatment as well as anticipation of emergencies is necessary.

The use of drugs, especially neostigmine, as well as other forms of therapy will be considered in this paper.

NEOSTIGMINE

According to Oppenheim,[1] several authors in the 1890's suggested that physostigmine might be an effective drug for the treatment of myasthenic weakness. In one instance a patient was given an unknown amount of physostigmine but was reportedly unable to tolerate the side effects of the drug. Mary Walker in 1934[2] working on the same assumption, namely that fatigability in myasthenia gravis is due to a "curare-like poisoning of the motor nerve endings or of the myoneural junctions," found striking though

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not quite uniform improvement following the hypodermic injection of 1.0 to 1.25 mg. of physostigmine salicylate in one patient who was able to tolerate the side effects of the drug. The same author in 1935[3] was able to compare the effects of physostigmine and a synthetic analogue, neostigmine, in another patient. Neostigmine was found to be much less toxic than physostigmine, which has strong cardiac and respiratory effects. Nausea, vomiting and diarrhea were less marked with neostigmine than with physostigmine and could be counteracted by atropine. It was felt, at that time, that both drugs in some way protect acetylcholine from premature destruction by what is now known to be a specific esterase.

The precise relationship of acetylcholine, cholinesterases and anticholinesterases in the mechanism of transmission of the nerve impulses at the neuromyal junction is not yet clearly understood in spite of a large number of highly fruitful and important investigations.[4] However, it has been shown that physostigmine and neostigmine are actually inhibitors of cholinesterases. Furthermore, a systematic search for substances possessing anticholinesterase activity has led to the discovery of several new compounds, mostly alkyl phosphates, with a distinctly favorable effect on myasthenia gravis. The majority of them are of little or no clinical use because of a high degree of toxicity.

Neostigmine has remained the most important drug in the treatment of myasthenia gravis. It is available in two forms: as methylsulfate in solution, usually 1:2000 for parenteral use, and as hydrobromide for oral use in tablets of 15 mg. Following a subcutaneous injection of 1.0 to 1.5 mg. of neostigmine methylsulfate, the untreated patient with myasthenia gravis of average severity experiences relief of weakness within 10 to 15 minutes and the effect lasts for three to four hours. Intravenous injection produces this effect more quickly, but it is usually unnecessary. The average oral dose of neostigmine bromide is 30 mg. (two tablets). The action of the drug is manifest within 20 to 30 minutes and the effect again lasts for three to four hours. Dosage requirements vary with age, severity of the symptoms, the amount of physical activity, and the distribution of the weakness. Larger doses are required especially when there is involvement of muscles serving vital functions of breathing and swallowing. The average oral dose of 30 mg. is repeated every three or four hours while the patient is awake. Patients with severe weakness may require 60 mg. every two hours. In some cases, especially with respiratory weakness, the medication must be given throughout the day and night. Patients who are unable to swallow the first morning dose after awakening should receive at least one dose in the middle of the night. Other patients may require an injection of neostigmine methylsulfate on awakening; still others may need injections before each meal in order to enable them to eat adequately even though they receive maximal oral medication. In cases of intractable dysphagia, feeding by nasogastric tube may become necessary.

Many patients have learned to adjust the amount of neostigmine to the varying daily needs, adding or omitting according to the activities they anticipate and the fatigue they experience.

Weakness of the extraocular muscles is often refractory to even large amounts of neostigmine. No attempt should be made to carry the treatment to extremes in order to relieve these symptoms, especially when there is an otherwise satisfactory general response to the drug. In cases where diplopia cannot be relived by medication, the patient should

be given blinders to be worn alternatingly in order to avoid amaurosis "ex anopia." Crutch glasses have been designed to correct ptosis.

Failure to respond to neostigmine in one system or a general refractoriness may develop at any time in the course of the disease, especially in the more severe cases, but generally the response to neostigmine in untreated cases is so unequivocal as to be almost specific. Conversely, the ability to tolerate large amounts of the drug has been considered specific for mysthenia gravis by some authors.

There are occasional patients with the classic clinical picture of myasthenia gravis who do not respond to neostigmine at any time. The question as to whether or not these patients should be properly classified as myasthenics is unanswered.

Toxic side effects of neostigmine occur in a majority of patients at least early in the course of treatment. They are rarely of a serious nature and most of the patients will later tolerate the drug without difficulty or need for compensatory medication. It may be necessary to take small amounts of food, such as milk and crackers, with the early morning dose or when the drug is given between meals. The side effects most frequently encountered are referable to the gastrointestinal tract: abdominal cramps, increase in peristalsis, diarrhea, nausea and occasional vomiting. Next in frequency are phenomena of glandular hypersecretion, most commonly of the bronchial mucosa and salivary glands but also occasionally of the sweat and lacrimal glands. Bronchospasm and, in sensitive subjects, asthmatic attacks are known to occur. Tachycardia, commonly seen with physostigmine, is encountered rarely. Tremor, incoordination and fascicular twitching of the muscles are seen occasionally. With a more severe form of reaction there may be spasm and "freezing" of muscles adding an unexpected form of muscular weakness. With large doses a paradoxical curare-like effect may occur. Except for the latter, most of the toxic effects in patients treated for myasthenia gravis are "muscarinic." They are prevented or treated by parenteral or oral administration of atropine sulfate, usually from 0.3 to 0.6 mg. per dose. Some patients prefer tincture of belladonna (5 to 20 drops per dose), the dosage of which can be more easily regulated. Synthetic derivatives of atropine have also been found useful. It should be remembered that in cases of respiratory weakness and inability to cough, atropine may have unfavorable effects. The use of the drug may lead to an increase in viscosity of bronchial secretion and additional respiratory embarrassment. In these cases the excessive secretion must be removed by tracheal suction.

In patients who are unduly susceptible to the side effects of neostigmine and in new patients who are given neostigmine in order to establish or exclude the diagnosis of myasthenia gravis, atropine should be administered 20 to 30 minutes before neostigmine is injected. In most cases, especially when neostigmine is used in tablet form, the two drugs can be given at the same time. Atropine may be omitted when neostigmine is taken with or shortly after a meal. While absorption of neostigmine is usually somewhat delayed by this method of administration, full therapeutic effect can be obtained by proper adjustment of dose.

ADJUVANT DRUGS

Several drugs, while not in themselves effective in correcting severe myasthenia gravis, have been found to potentiate the action of neostigmine. The most important of these is ephedrine sulfate, whose effect was discovered incidentally in 1930[5] when it was given in order to relieve dysmenorrhea in a myasthenic

patient. Its pharmacologic action in myasthenia is not fully understood; however, it does not appear to have a direct inhibitory action on cholinesterase. In some patients it appears to enhance and prolong the effect of neostigmine. In others it is entirely without benefit. It may produce tenseness, tachycardia and, when given in late afternoon, may lead to insomnia. The therapeutic dose is 25 mg., which may be repeated two or three times daily.

Potassium salts, especially the chloride and citrate, have been shown to lower the threshold of muscle fiber and postganglionic cell to electrical stimulation and to activation by acetylcholine. In spite of this apparently sound physiologic rationale, the clinical usefulness is limited by the renal threshold for potassium ions and by the gastrointestinal effects of doses in excess of 20 gm. per day. In some instances slight improvement in strength is reported by patients. It is used in 25 per cent aqueous solution and can be administered orally three or four times daily. The usual single dose is 8 cc.

Laboratory experiments indicate that guanidine hydrochloride increases the sensitivity of denervated muscle to acetylcholine. We have not seen any significant beneficial effects from the use of this substance, and gastrointestinal discomfort and paresthesias are common side effects. In one case, hematuria followed administration of this drug.

ALKYL PHOSPHATES

Several highly toxic substances, originally synthesized as insecticides or war gases, have a profound and longlasting anticholinesterase effect. Some of these compounds have been used in the treatment of myasthenia gravis. Di-isopropyl fluorophosphate (DFP)[6] and tetraethyl pyrophosphate (TEPP),[7] two of these compounds which have been given extensive study, have a narrow range between the therapeutic dose and that which produces serious central nervous system manifestations. TEPP, in addition, is unstable in the usual solvents. In spite of unequivocal improvement of myasthenia gravis which follows the use of these compounds, they are of limited clinical value and should be administered only under observation in the hospital.

One other substance in this group, octamethyl pyrophosphoramide (OMPA),[8] is stable in aqueous solutions and is relatively nontoxic. It resembles neostigmine in its therapeutic and side effects, but has the advantage that it need be given only twice a day at 12 hour intervals in order to maintain an even therapeutic effect. Its anticholinesterase action, as that of other alkyl phosphates, lasts for several weeks, and care must be taken to avoid cumulative effects. Suboptimal doses of OMPA may be used in combination with neostigmine. It should, however, be noted that some of the toxic side effects are potentiated when both drugs are administered at the same time. It is best to separate doses of the two drugs by an interval of about three hours. The same considerations apply in moderately severe cases when the therapy is changed from neostigmine to OMPA. In mild cases the change-over is quite easy. OMPA is administered orally in doses from 7 to 15 or 20 mg. twice a day. Muscarinic side effects are controlled with atropine sulfate. Some observers have stated that patients who fail to respond well to large amounts of neostigmine will derive no benefit from OMPA. In a series of 14 cases we have been impressed by the degree of improvement of some patients who were given OMPA.

Toxic responses to OMPA, neostigmine or other anticholinesterases, when given in maximal doses, may in rare cases be mistaken for exacerbations of myasthenia. "Cholinergic crises"[9] are avoided or con-

trolled by prophylactic use of atropine, if necessary, in doses of 1 mg. or more.

TENSILON

Recent observations[10] on Tensilon, a neostigmine analogue, seem to indicate that this substance has an anticurare effect without any significant anticholinesterase action. It has been recommended as an aid in establishing the diagnosis in doubtful cases. Intravenous injections of 10 mg. may relieve myasthenic weakness within 20 or 30 seconds. Intramuscular injection of 25 to 50 mg. apparently leads to improvement of weakness lasting for several hours. The toxic side effects of Tensilon are similar to those of the other drugs.[11]

ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE

The majority of patients who have been treated with corticotropin or cortisone have shown a definite decrease in strength during the period in which the drug was administered.[12,13] Several observers, however, have noted significant improvement in the period following the completion of therapy. It has been stated that improvement lasts for several weeks or even months. Other observers have reported no beneficial effects from the administration of these hormones and this is in accord with our experience. One case has been reported in which myasthenia gravis developed during prolonged cortisone administration in a patient suffering from rheumatoid arthritis.[14]

THYMECTOMY

Since 1901, it has been known that abnormalities of the thymus occur in about 20 per cent of cases of myasthenia gravis. These abnormalities include benign and occasionally malignant thymomas, hyperplasia of histologically normal glands, and persistance of the gland well into adult life. The etiologic connection between thymus and myasthenia is far from clear. Most cases of myasthenia show no gross abnormality of the thymus, and thymomas can be present in patients who do not have myasthenia gravis. In one of our own cases, a thymoma was found incidentally in a routine examination of the chest. Five years after surgical removal of the tumor the patient developed the first signs of myasthenia.

In spite of the lack of evidence of causal relationship betweent thymus and myasthenia gravis, a high incidence of partial or full remissions following surgical removal of normal or neoplastic thymus glands has been described in reports from several clinics,[15–17] and serious consideration must be given to the value of this approach to the treatment of myasthenia gravis. In a large series of cases reported from the Mayo Clinic it was found that the clinical course of patients in the operated group was considerably better than that of a similar group adjusted for age, sex and severity of disease. Fifty per cent of the operative group were improved as a result of the surgery, while only 29.2 per cent of the control group had comparable spontaneous partial or complete remissions. The authors of the Mayo Clinic report are still not entirely convinced that the selection of cases for operation may not have played some role in the more favorable outcome in the operated cases. Moreover, many cases are on record where death from myasthenia occurred after complete removal of all thymic tissue. The presence of a thymoma seems to influence the course of the disease unfavorably whether the tumor is removed or not.

THE MYASTHENIC CRISIS

Sudden death from apparent respiratory failure at the time of an apparently satisfactory remission is a well-known feature of myasthenia gravis. In other cases progressive weakness of muscle of

respiration may occur in spite of the administration of increasingly large amounts of neostigmine and lead to a respiratory crisis. In our own series of 156 cases, fatal crises occurred in 20 and nonfatal crises in 16 cases. Whenever it is possible to anticipate this event, a tank-type respirator, tracheotomy set, oxygen equipment and suction apparatus should be available. Following tracheotomy the patient is placed in the respirator and oxygen administered as needed. Neostigmine is withheld, atropine administered judiciously to keep the airway dry, and suction is employed to keep it open. For the average adult the respirator is set for a negative pressure of 15 pounds per stroke and for 16 to 20 strokes per minute. This may be modified in order to avoid overventilation and alkalosis. Electrolyte balance is maintained by infusion, especially in patients who are dehydrated due to dysphagia or as a result of diarrhea secondary to the toxic effects of neostigmine. Sedatives may be administered and morphine may be beneficial while respiration is maintained mechanically. Antibiotics in doses sufficient to prevent pneumonia should be given. After a few days it is usually possible to stop the respirator temporarily without removing the patient from it and later on the patient can be allowed out of the respirator for increasing periods as tolerated. A gratifying number of patients who survive a crisis undergo remissions, some of which have lasted for several years. Successful management of a myasthenic crisis requires experienced personnel and 24 hour nursing care.

Patients who live too far from the hospital to be brought in quickly when a crisis occurs, should be given a written statement to be used by a local doctor unfamiliar with the disease and possibly by the fire department or similar agencies owning a respirator. The statement should describe in simple terms the nature and dangers of mysathenia gravis. A responsible member of the family should be instructed in the use of a syringe, and neostigmine methylsulfate should be available to all patients who have no easy access to medical care.

PROGNOSIS IN MYASTHENIA GRAVIS

In our own series of 156 patients, 95 were followed for periods ranging from one to 21 years (average 5.7 years) or to death. Fifty-eight of these 95 patients are living. The average duration of illness after onset of symptoms has been 7.6 years. Thirty-seven patients have died. Fourteen of the 37 (38 per cent) died within one year of the onset of symptoms and 19 (51 per cent) died within two years. The average duration of life after onset of symptoms in this group was 3.1 years. It is our distinct impression that the first two years in this illness represent the most critical period, and that after this the chance of survival increases considerably. There was no sex difference in the mortality rate of patients with the onset of the illness between the ages of 11 and 50 years since 18 of 61 female patients and five of 15 male patients died of the disease. On the other hand, however, it shoud be pointed out that in our own case material, as in that of others, the morbidity for women in the sexually mature period (15 to 45 years) is strikingly higher than that for men with a preponderance of more than 3.1. In contrast to this, we have four male and no female patients under age ten, while we have 20 male and 13 female patients over 50.

Spontaneous remissions occurred in 33 of the 95 patients in the follow-up group. A few patients had several remissions, partial or complete, with relapses in between. Seven patients died in relapses, four after complete and three after partial remissions. Remissions occurred within one month after onset of the illness in

two cases and lasted for 30 and ten months, respectively. The latter of the two patients, following relapse with crisis, had a second complete remission six years after onset of the illness and has been completely free of symptoms for over four years. In one instance a complete remission occurred 19 years after onset and lasted for six years.

It is often stated that pregnancy has a beneficial effect on the course of myasthenia gravis. Our own experience in this respect is not uniform. Twenty-two women in our follow-up series had 27 pregnancies. In nine there was a partial or complete remission of symptoms. In five the severity of the illness was not affected by the pregnancies. On the other hand, exacerbations of many symptoms occurred in eight women coincidental with pregnancies and necessitating therapeutic abortions and, in one instance, premature delivery.

Many women reported spontaneously or upon direct questioning a slight premenstrual "slump" during which it was occasionally necessary to increase the dose of neostigmine. We do not have sufficient data in regard to the effect of menstruation to draw any conclusions. In two patients Estinyl was administered in doses sufficiently large to suspend menstruation without effect on myasthenic weakness.

Many patients have been able to lead fairly normal and active lives taking neostigmine. In other instances it was possible to protect them during exacerbations of the illness until spontaneous remissions occurred. In conclusion it must be stated, however, that the disease is quite unpredictable, that our knowledge of its etiology is quite unsatisfactory, and that our empirical approach to its control is not always successful.

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CLINICAL PATHOLOGIC CONFERENCE

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CASE PRESENTATION

A 54 year old man was admitted to the hospital on March 7. Since the patient was semicomatose and unable to respond to questions on admission, the history was obtained from his family. He had had chronic bronchitis and asthma for many years, raising a moderate amount of sputum, but had seldom missed work because of his health. He carried on his trade as a shoemaker until two weeks prior to hospital admission when he collapsed on the street and was brought home. It was not known if he had lost consciousness. On reaching home he had severe shortness of breath and coughed a great deal, raising large amounts of mucoid white sputum, not blood-stained. He had to sit in a chair most of the time to get his breath. After being home for one week he was able to return to work, but two days before admission he again had to leave his work because of increasing shortness of breath, general malaise and weakness. The day before admission, cough and dyspnea increased, the sputum became pinkish, and he complained of "back pain" aggravated by breathing. He spent most of the day in a chair because sitting up helped his breathing. Later in the evening he was taken to a local physician who advised hospitalization. During the night the patient became lethargic and appeared to have difficulty in speaking. On the day of admission he became comatose.

The only additional bits of information were as follows: the patient had had attacks of dizziness for two or three months; he had lost 24 lbs. in weight during the past year; he ordinarily smoked two packages of cigarettes each day and had formerly been a heavy drinker; he had had a herniotomy in 1941; his particular work, "bottom finishing" of shoes, exposed him to a great deal of dust mixed with dyes and wax; there was no history of familial disease.

Physical examination: Temperature 102° (R); pulse 140/min.; respirations 34/min.; blood pressure 110/70. On admission the patient was semicomatose, emaciated, obviously dyspneic, moderately cyanosed, and subject to an aggravating cough which failed to clear his airways of thick mucus. He lay quietly and was unresponsive except for slight stirring when a painful stimulus was administered. Occasionally, if disturbed sufficiently, he mumbled "all right."

The nose and throat were not remarkable. The right ear drum lacked luster while the left was obscured by wax. The neck veins were not engorged. Breathing was labored, deep and rapid. Respiratory excursion was decreased at both bases, more on the right. Dullness to percussion was present over the right middle and upper lobes where coarse sticky rales and a leathery friction rub could be heard. The heart was rapid but of normal sinus rhythm and there were no murmurs. Abdominal and rectal examinations were not remarkable. There was no clubbing of the fingers, glandular enlargement or skin rash. All four pulses were present at the ankles.

From the Montreal General Hospital and the department of neurology, McGill University Faculty of Medicine.

Nervous system: The patient moved all four limbs spontaneously and equally. The pupils were small, regular, equal, and reacted to light. The fundi including disk, vessels and retina were not remarkable. The extraocular movements seemed full, and no nystagmus was observed. The face appeared symmetrical and the corneal and gag reflexes were present. There was no obvious weakness of the limbs or any adventitious movement. The response to pin prick was equal on the two sides. The tendon reflexes were all present and equal although less brisk than usual. The plantar response was bilaterally downwards. The head was held moderately extended, and mild rigidity of the neck was felt.

Course and laboratory examination: The admission diagnosis was pneumonia, and an immediate roentgenogram of the chest showed an extensive pneumonic infiltration of the right upper and middle lobes. A smear of the sputum demonstrated clumps of gram-positive cocci but no tubercle bacilli. The next morning the sputum culture showed staphylococcus pyogenes, sensitive to penicillin. Urinalysis was not remarkable, acetone being absent. The blood count was as follows: RBC 5.4 million, WBC 23,400, hemoglobin 80 per cent, differential: polymorphonuclears 77, lymphocytes 23. The stool benzidine test was 3+. The blood sugar shortly after an intravenous infusion was 238, later 151; the blood urea nitrogen 64, repeated, 66. The carbon dioxide combining power was 53; the Kline exclusion test negative. Three blood cultures showed no growth.

A lumbar puncture was done shortly after admission and revealed an initial pressure of 170 mm. and crystal-clear colorless fluid containing 6 cells per cu. mm., nearly all lymphocytes. The Pandy test was negative. Culture of the fluid showed no growth. Determinations of the protein and sugar were not made.

The patient was almost moribund on admission, so penicillin 300,000 units q3h, streptomycin 1.0 gm. q6h, and terramycin 500 mg. intravenously q8h were started. During the next 24 hours he became somewhat less responsive. Roentgenograms of the skull were not abnormal, but the pineal gland was not seen. On March 9, two days after admission, the patient was in deep coma with marked extension of the neck. The limbs showed increased rigidity but the plantar responses were still down. On tapping the patellar tendon, flexion of the right great toe took place regularly. In spite of this worsening of the neurologic status, the temperature had fallen almost to normal and breathing was slower. On March 10, the temperature was normal and respirations were 16 per minute. A chest roentgenogram showed remarkable resolution of the pneumonic process. However, coma deepened and there was a tendency to opisthotonos. The left optic disk was hazy but there was no papilledema. There were no lateralizing signs at any time. The patient's temperature began to rise again and on March 12 it reached 104° F. On March 13 respirations had increased to 45 per minute and the patient was deeply unconscious. A repeat lumbar puncture was done. The tap was an easy one, but after five drops were obtained the patient suddenly expired. The fluid which was clear and acellular was under an initial pressure of 150 mm., and the Pandy test was negative.

DISCUSSION

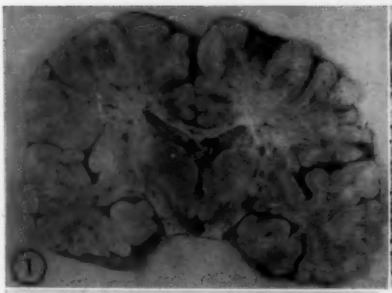
The clinical picture presented here was one of chronic pulmonary disease and a superimposed acute episode complicated by coma which worsened as the acute pulmonary lesion improved. Initially an acute meningitis, possibly pneumococcic, was suspected but the presence of only six cells, chiefly lymphocytes, in the cerebrospinal fluid excluded that diagnosis. Tuberculous meningitis complicating chronic pulmonary tuberculosis also had to be ruled out, the absence of tubercle bacilli in the sputum being strong evidence against such a diagnosis. Too, the cell count of the spinal fluid is usually but not always higher in tuberculous meningitis. Furthermore, the initial cerebrospinal fluid pressure was approximately normal (170 mm.) and the Pandy test negative. Protein and sugar determinations were not done, since nearly all fluid was used for bacteriologic purposes. It might be remarked here that diagnosis of many neurologic cases is made more difficult because of failure to obtain all the desired information from the first lumbar puncture. It is absolutely essential to

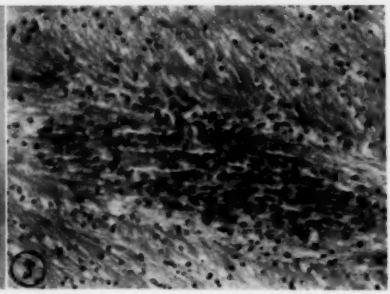
plan carefully the diagnostic uses of the fluid so obtained.

In view of the failure to establish the diagnosis of meningitis, several further possibilities were entertained, including brain abscess (single or multiple), septic embolism, metastatic bronchogenic carcinoma, thrombophlebitis, and even a subdural abscess. The spinal fluid picture would have fitted any of these. There is a tendency for students to learn that up to seven or ten lymphocytes in the spinal fluid is normal. This is quite in error since there is usually no more than one, and certainly six is abnormal. At no time were there localizing signs, and it is unlikely that a single brain abscess could cause death in coma without betraying itself by some localizing feature. Multiple brain abscesses as a rule do not run such an abrupt, fatal course, particularly under antimicrobic therapy. Also there would have had to be a great many small abscesses present or localizing signs would have appeared. Such an abundance of small abscesses does not occur secondary to lung disease. Septic embolism from acute endocarditis can produce the entire clinical picture, but there was much evidence to the contrary—namely, persistently negative blood cultures, the absence of cardiac murmurs, and the lack of embolic phenomena elsewhere (skin, kidney, eye, and so on). Secondary cancer from the lung was never ruled out entirely. The presence of emaciation and chronic pulmonary disease were suggestive of that possibility, but rapid onset of coma would have to be accounted for by a strategically-placed midbrain lesion. Yet no localizing neurologic signs appeared. Hemorrhage into a secondary deposit was unlikely in view of the absence of xanthochromia in the cerebrospinal fluid. Finally the chest film did not suggest a tumor.

In considering the presence of an expanding lesion the nature of the final episode became of interest. The occurrence of death during a lumbar puncture was probably purely coincidental, since the patient was seriously ill. However, the possibility of a cerebellar pressure cone or a transtentorial temporal herniation came to mind. Thrombophlebitis (sinus or superficial veins) must always be kept in mind in cases of obscure intracranial disease. Again, profound coma without localizing signs, in the absence of raised intracranial pressure and seizures, was against phlebitis. It is not clear if the left ear drum was visualized at any time (it was obscured by wax initially), but at any rate it was assumed to have been normal. Mastoiditis and sinusitis were not seen in the roentgenogram of the skull (which unfortunately failed to show pineal or habenular calcification just when it was badly needed) so that most evidence was against thrombophlebitis. For the same reason, i. e., lack of source, a subdural abscess was not considered seriously, particularly with the additional unlikelihood that such an abscess could, while being treated with penicillin, lead to deep coma without producing lateralizing signs.

As one diagnosis after another failed to hold, the opinions, particularly those of the internists, turned to metabolic disorders, in spite of the presence of neck stiffness and an abnormal spinal fluid. The blood sugar level was initially raised to 238, but later fell to 151, and there was no acetone in the urine, so diabetic coma was thus ruled out. The blood urea nitrogen, for some unexplained reason, was in the 60's on two occasions but uremia of that order never produces coma by itself. In acute hypertensive encephalopathy with coma the blood urea level may be no higher, but then hypertension and brain edema are the responsible factors. Once when the blood pressure fell to 90/60 the possibility of adrenal insufficiency was entertained, but apparently not seriously, for the electro-





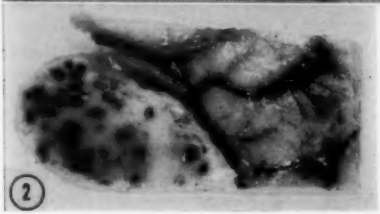


FIG. 1. Cross-section of brain showing abundant small hemorrhages and hemorrhagic stains in the white matter.

FIG. 2. Sagittal cross-section of corpus callosum showing hemorrhages.

FIG. 3. Microphotograph of one of the focal non-hemorrhagic lesions.

lytes were not determined. Hypernatremia, hyperchloremia and coma secondary to a hypothalamic disorder were only mentioned.

In the meantime, all the causes of coma were methodically discussed and rejected one by one, including hepatic disease and barbiturate intoxication. Encephalitis of viral origin (equine, St. Louis, and so on) has not been described in this region since the epidemic of Von Economo's disease in the 1920's, so that we tend never to make such a diagnosis. Postinfectious encephalomyelitis, while usually following a viral infection such as measles, chickenpox, smallpox, or influenza, can occur apart from any such clinically recognizable infection, and in the case at hand the patient had had the first evidence of sickness two weeks before the onset of coma. This then was a distinct possibility, without any means of proof or disproof. Finally there was as a last resort "coma of undetermined origin." Our neuropathologist reports that there is a constant trickle of cases of coma in which a detailed clinical and pathologic study fails to reveal any metabolic or anatomic substrate. However, in those cases the spinal fluid was always normal.

It was most distressing in this case to watch the patient's coma deepen as the pulmonary disease improved. Although a diagnosis could not be made, it was considered that surgically-treatable disease of the brain had been excluded, and that heavy doses of antimicrobic agents provided the best and only therapeutic hope.

Final Clinical Diagnosis:

1. Pneumonia — improving.
2. Coma of undetermined origin.

Pathologic Diagnosis:

1. Brain purpura.
2. Resolving staphylococcal (pyogenes) bronchopneumonia of right lung.

PATHOLOGIC FINDINGS

On external examination, the brain was perhaps a little swollen but otherwise not remarkable. The pia arachnoid was thin and translucent. The

veins and sinuses were normal. There was mild coning of the undersurface of the cerebellum, deemed of no significance. The large vessels at the base were free of atherosclerosis.

Upon section there were innumerable small hemorrhages and hemorrhagic stains throughout the white matter of the brain, the cortex being entirely spared (figure 1). The hemorrhages ranged in size up to 4 mm. and were most abundant in the occipital lobes and corpus callosum. The convolutional white matter seemed more affected than the deeper central white matter.

Microscopically, the presence of recent hemorrhages of all sizes was confirmed. When the hemorrhage was adjacent to a small vessel the latter was almost obscured, but other hemorrhages formed a neat ring in the perivascular space around larger arteries up to 300 μ. There was no tendency to a perivenous localization. Not uncommonly, lesions consisted chiefly of a focal collection of unidentified cells, showing only a large rounded pale nucleus with scattered chromatin granules, reminiscent of astrocytes, but a scattering of red cells were present also. A small number of macrophages ballooned with ingested red cells could usually be seen. The myelinated fibers were pushed aside or displaced by the hemorrhages and associated edema, the picture not being suggestive of a primary demyelinating disease.

COMMENT

Brain purpura or hemorrhagic encephalitis was formerly well known because of its tendency to complicate arsphenamine therapy. However, the condition occurs quite unrelated to arsenic therapy. Although its exact nature, cause and pathogenesis are obscure, it has been reported in association with many infections and various drugs. No definite statement regarding the responsible agent in this case can be made as the details of medication before admission to hospital could not be ascertained accurately. The clinical course is usually brief (a week or less) and is characterized by confusion, stupor and coma without lateralizing signs, ending in death. It is, of course, not known if milder cases recover since the diagnosis cannot be established clinically with certainty, but not all postarsphenamine cases ended fatally. No therapy is of avail. The other organs of the body are spared as a rule. The pathologic aspects of the disease have been discussed by Alpers[1] and by Russell.[2] Brain purpura must always be kept in mind in cases of unexplained coma. It is not a rare disease by any means, and is of theoretical interest as it probably represents a form of cerebral allergy in which the reaction is localized to blood vessels of the white matter. As a disease of white matter, it is of interest to students of demyelinating processes.

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Neurology BOOK REVIEWS

The Autonomic Nervous System

Albert Kuntz, Ph.D., M.D. Fourth edition. 1953. Philadelphia: Lea & Febiger. 605 pages. $10.00.

The Autonomic Nervous System by Doctor Albert Kuntz, professor of anatomy in the St. Louis University School of Medicine, represents over three decades of devoted study of the subject. The fourth edition brings into sharper and clearer focus than ever before the immense amount of painstaking observvation undertaken by the author and his numerous co-workers and students. Had the author so chosen, this could have been expanded into a volume many times its size; but, to the great benefit of his readers, he has eliminated much detail, particularly in the older contributions, and, through concise style, has epitomized the vast amount of recent and current material. This will be especially appreciated by the clinician who frequently needs a rapid source of information.

This work, authoritative in its presentation of the morphology of the autonomic nervous system and the central autonomic centers and conduction pathways, presents the whole story of this division of the nervous system – history, embryology, general physiology and special physiology, with detailed reference to the heart, respiratory, blood vessels, digestive system with its accessory organs, urinary and sex organs, skin and endocrine system. This material presented in the first portion of the book serves as a firm foundation for the second portion which deals with the clinical applications. The chapter on the histopathology of the autonomic system may be singled out for special comment. The difficulty of determining the presence or absence of pathologic changes of a fine degree in material removed at operation and autopsy is a problem well known to pathologists. Kuntz has assembled an impressive amount of material and, by making use of a battery of histologic and the new histochemical technics, has established a basis for more accurate estimates of pathologic states in routine hospital laboratory diagnosis.

The handling of the important pain and other sensory pathways from the blood vessels and viscera is one of understanding and clear literary presentation . . . a point not to be overlooked by teachers on the subject who find their students frequently confused by unnecessary semantic difficulties largely created by the terminology of the early English physiologists.

In treating of the autonomic nervous system in disease, each organ involved is discussed separately. The range of information conveyed in these chapters is extensive, and the author constantly integrates basic anatomy and physiology with pathologic and diagnostic factors. He has collaborated closely with neuro-

surgeons, so that the presentation of autonomic neurosurgery is well oriented clinically and serves at every turn to give illustrative examples of the fundamental observations described in the first portion of the book.

This work is in the tradition of the great monographs. It presents the whole picture: history, development, basic science, and clinical applications, all directed toward practical use in man. Whether the neurologist deals primarily with the medical or with surgical aspects of the autonomic nervous system, the omission of this book from his library would be a serious one. A. R. V.

Diagnostic Tests in Neurology: A Selection for Office Use

Robert Wartenberg, M.D. 1953. Chicago: The Year Book Publishers, Inc., 228 pages. $4.50.

In this little book Dr. Wartenberg presents, in a lucid and graphic manner, a large assortment of tests that are of value in the appraisal of the neurologic patient. He stresses the fact that these are exclusively clinical diagnostic tests which can be performed easily in the office and at the bedside and without recourse to laboratory procedures. The author deplores the present tendency to overload neurologic diagnosis with mechanical, technical and laboratory routines, and makes a plea for the return to purely clinical observation in diagnosis. In his own extensive undergraduate and postgraduate teaching on two continents, he has always stressed "clinical sense" based on observation and judgment, and in this book, written in simple language and profusely illustrated, he presents to the general practitioner of medicine and the physician who does not specialize in neurology the fruits of his long years of experience.

The tests described include those dealing with the cranial nerves, the pyramidal and extrapyramidal systems, the cerebellum, the sensory system, and the vasomotor-trophic apparatus. Many of the procedures and methods of examination described are well known and generally employed, but some bring out diagnostic criteria that even the most experienced neurologist may profit from. The book is packed with valuable suggestions.

The present reviewer can list only three criticisms. The tests are oversimplified, and the inexperienced clinician may find observation more difficult than he would expect from the descriptions in the text. While the underlying anatomic and pathophysiologic bases for the findings in disease states are sound, they are referred to somewhat superficially and incompletely. The facility of description and stated pathognomonic nature of the tests may impress on the mind of the naive reader that a specific diagnosis can be made on the basis of a single test, rather than relying on a complete examination in which a single test, as a significant part of the total picture, aids in confirmation of the diagnosis.

In spite of these objections, which may be raised in regard to any approach to didactic teaching, this is a valuable little book for every neurologist as well as for the general physician. Dr. Wartenberg's introduction alone, which is an expression of his creed and philosophy, gives the book inestimable value and should serve as a goal for every clinical neurologist, while the book itself might be termed the neurologist's *vade mecum*.

R. N. DE J.

The Grassi Block Substitution Test for Measuring Organic Brain Pathology

Joseph R. Grassi. 1953. Springfield, Illinois: Charles C Thomas, Publisher. 75 pages. $3.00.

In his preface Mr. Grassi states that his interest is in "the psychological behavior of the individual, particularly that behavior which can be investigated objectively by psychometric tests specifically designed to elicit evidence of organic involvement." To this end he presents a version of a block design test employing the multi-colored Kohs cubes in which the subject must reproduce from actual models a series of five four-block designs. Each of the models is to be copied in terms of the top surface only and three dimensionally as well; the instructions also call for the reproduction of the same patterns with complete change of color, again in terms of first one, and then three dimensions. The instructions may be modified as necessary to insure the subject's understanding of the tasks set. Scoring is on the basis of elapsed time for each problem, with one point credit for completion within 120 seconds or less, a bonus of ½ point for a difference of less than ten seconds between the times for any two successive steps, and a penalty of ½ point for any design not completed within the time limit.

The author feels that this procedure will discriminate between "early" (abstract) intellectual impairment evident only in failure to reproduce designs with color changed and "late" (concrete) intellectual impairment which will show in failure to copy as well, especially on the three-dimensional level. He states that the designs have been so chosen that failure cannot be explained on the basis of intellectual deficit alone though he suggests that the technique not be used with patients having a Wechsler-Bellevue IQ rating below 70. Actual size color prints of the designs and a rather elaborate record sheet including norms are reproduced in the text.

In his theoretical discussion Mr. Grassi pays tribute to the work of Goldstein and Scheerer whose cube tests served as a point of reference for the development of his own technique, which he regards as a refinement since, according to his thesis, it differentiates between "concrete" and "abstract" requirements. His method of having the subject copy from an actual model appears a revival of the "Cube Construction Test" principle described on page 72 of the "Examiner's Guide for Psychological Examining in the Army" published in September 1917 and July 1918.

The standardization was done on 274 subjects: 86 "normals," 86 "schizophrenics," of whom 43 are described as "deteriorated," 72 "organics," and 30 "postlobotomy." The reliability was determined by the re-test method which yielded a reliability coefficient of .85. In spite of his expressed reluctance to place much reliance on the test score alone, the author presents the findings on the four groups in terms of both range and mean test score for each.

To validate his claim that behavioral analysis during testing is of greater importance than the formal rating, he presents in detail a total of 11 illustrative cases drawn from the first three groups with the addition of one mentally defective individual and a four test series covering a year's time on one of the postlobotomy subjects. The protocols of these individuals are discussed in detail in terms of the ten indicators of organic impairment which he cites in his chapter on "Interpretation."

Experimental enterprise is most praiseworthy and much work should be done in the area of determining the objectively reportable evidence of incipient organic impairment of intellection, but in the absence of further information concerning the actual experimental and statistical procedure this reviewer is not convinced that Mr. Grassi has succeeded in doing this definitely. From his own statements it is apparent that he is himself aware of the tentative nature of his present data, for many of his conclusions are stated as generalizations. C. E. C.

A Stereoscopic Atlas of Human Anatomy
Section 1. The Central Nervous System

David L. Bassett, M.D., with photography by William B. Gruber. Portland, Oregon: Sawyer's, Inc. 500 pages. 238 stereoscopic views mounted on 34 View-Master reels. $27.50. Viewing equipment extra.

This work by Dr. David L. Bassett, associate professor of anatomy at Stanford University, presents the structure of the human central nervous system in three-dimensional color, utilizing the View-Master stereoscopic transparencies. The resulting visual perception is brilliant. Making use of injected latex, red for arteries and blue for veins, the vascular system stands out with great prominence and detail; a quick survey is afforded of the relations and distribution of the individual blood vessels.

The truly amazing number of structures that can be demonstrated by careful gross dissection has long been a fact known, it seems, only to classroom teachers of neuroanatomy. This work, however, presents the truth to all: many readers will experience a new and satisfying intellectual pleasure in seeing in three-dimensional clarity pathways such as the mammillo thalamic tract, the fasciculus retroflexus, the internal medullary lamina of the thalamus, the dorsal longitudinal fasciculus, and numerous other structures which are generally thought to be visible only in a series of stained sections.

The text presents, on the page to the right, an outline drawing of each dissection with structures numbered, and on the page to the left, a brief description of the dissection and an identification of the numbered structures. The viewing equipment is reasonably priced. The reviewer recommends a battery type outfit which has constant illumination and can be manipulated readily while the book is spread open for reference.

In medical colleges where there is a dearth of material for dissection, access to this work would be of great value to students. It forms an almost perfect way of reviewing neuroanatomy for special board examinations. To the neurologist and neurosurgeon it gives a rapid, accurate way of scanning a structural area and a comprehensive demonstration of anatomic relations in a proposed operative field.

The transparencies can be projected in two-dimensional form for classroom use. The section on neuroanatomy is one of seven proposed sections presenting the entire human body. It can be said that this work is a noteworthy contribution to the morphologic sciences. Neurologists are fortunate in being presented with the basic anatomy of their subject several years before their less fortunate brethren in other special fields. A. B. V.

Neurology

Greater Superficial Petrosal Neurectomy for Orbitofacial Pain

Preliminary Report

William V. Trowbridge, M.D., John D. French, M.D. and Allan E. Bayless, M.D.*

GREATER SUPERFICIAL petrosal nerve section in the treatment of unilateral headache was first reported by Gardner in 1947.[1] A total of 26 patients underwent this surgical procedure in an attempt to control a variety of types of unilateral head pain. The reported results showed a wide range of relief, some patients reporting no improvement and others having complete cessation of their distress. Since a substantial number were completely relieved of their painful attacks, an analysis of these and other cases seemed to be in order, so that the proper place might be found for this procedure in the neurosurgical armamentarium. Operative section of the greater superficial petrosal nerve is established on firm physiologic ground in the treatment of the "syndrome of crocodile tears"[2] and bullous keratitis.[3] It has not found wide use, however, in the management of unilateral, episodic headache.

A review of Gardner's results indicates that patients with a certain stereotyped group of complaints seemed to obtain excellent relief from section of the greater superficial petrosal nerve. These complaints were sufficiently

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constant in their association and, therefore, a definite syndrome differentiating this group from other forms of hemicrania is suggested. The seemingly constant manifestations responding favorably to the procedure are as follows: 1) recurrent attacks of severe pain limited to one side of the head; 2) knife-like, cutting pain, predominantly retrobulbar in location; 3) intense, drenching lacrimation and conjunctival injection during attacks, both limited to the ipsilateral eye; 4) primarily nocturnal attacks.

During the past year four patients complaining of the described distress have come under the authors' care. In the absence of any other logical therapeutic approach, petrosal neurectomy was performed on this small group. It is the purpose of this report to present the effects of our efforts as seen during a short postoperative follow-up.

SURGICAL TECHNIC

The operative approach to the greater superficial petrosal nerve is essentially identical to that used in the extradural approach to the fifth cranial nerve.[1,3] Through a subtemporal craniectomy, the dura is dissected from the floor of the middle fossa until the middle meningeal artery is seen entering the skull through the foramen spinosum (figure 1). Dissection is then directed posteriorly toward the petrous pyramid until the greater superficial petrosal nerve is seen lying in a small groove on the floor of the middle fossa. The nerve may be traced posteriorly to the point where it enters the skull through the hiatus fallopii. It may be traced likewise, if desired, to the point where it disappears behind the Gasserian ganglion or the third division of the trigeminus. The nerve is readily sectioned in its small groove with a ganglion knife. The middle meningeal artery need not be divided. Tugging on the petrosal nerve should be avoided since this may easily precipitate a facial palsy.

CASE REPORTS

Case 1. — A 32 year old white man suffered a head injury in 1944 when a shell exploded near him in military combat. He was rendered unconscious for about five days following the injury. After regaining consciousness he began to suffer from transient attacks of deep facial pain on the right side. These appeared first as a dull ache in the supraorbital region. Suddenly a sharp, lancinating retrobulbar pain would appear and persist in intense form for two or three hours. During this latter pain there was intense lacrimation limited to the right eye. Simultaneously, the conjunctiva on the right side became bright red in appearance. These attacks appeared at irregular intervals, but usually occurred three or four months apart. In the four months prior to hospital admission, however, the patient experienced attacks every night. Although they occasionally occurred during the daytime, they usually appeared late at night, awakening him from sleep. He found it impossible to work, since he was awake most of the night with pain and was too tired to go to his job in the morning. He knew of no circumstance by which an attack could be precipitated, nor had he found any way to obtain relief of the pain. Histamine administered by a private physician had failed to precipitate an attack. The pain was unaffected by codeine.

The general physical and neurologic examinations revealed no abnormality, nor was any disturbance apparent on definitive examination of the eyes. Electroencephalogram and skull

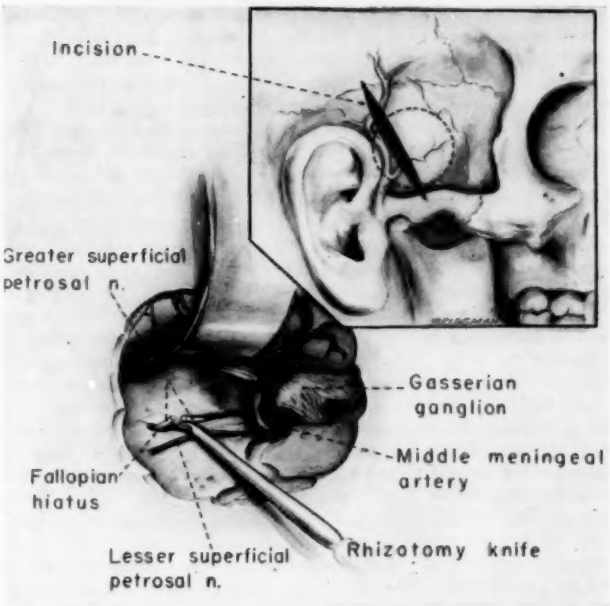

FIG. 1. Operative approach for section of the greater superficial petrosal nerve.

films were normal. Psychologic testing was reported as showing "situational stress in a relatively normal individual." X-rays of the cervical spine were normal.

On August 26, 1952 a greater superficial petrosal neurectomy was performed on the right. The postoperative course was entirely uneventful. The patient had no further episodes of pain, and was entirely symptom free when seen eight months after operation.

Case 2. – A 56 year old white man entered the hospital complaining of pain radiating from the right side of the nose to a retrobulbar position and into the right upper central incisor. He had been having such attacks intermittently over a period of seven years. The attacks ordinarily lasted about 45 minutes, and were quite infrequent when they first appeared. During the years previous to admission, however, these episodes occurred more frequently, varying between two and three attacks each night, with occasional free intervals of one or two days. Attacks were primarily nocturnal, although occasionally such episodes occurred during the day. During periods of pain, the original dull aching component slowly changed to a sharp, lancinating, "cutting pain behind the eyeball." The right eye became very red and tears poured from it. The patient stated that the pain was unbearable during the greatest intensity of the attacks. At the onset of these episodes, seven years previously, a sinus operation was performed but gave him no relief. Nothing was known which could precipitate or relieve an attack. There was never any pain on the left side of the face. Attempts to precipitate such episodes with histamine had been unsuccessful. Ergot derivatives and opiates gave no relief during pain.

The general physical examination was entirely negative. Neurologic examination was normal except for the presence of a classic Horner's syndrome on the right side. Extensive

clinical and laboratory examinations failed to reveal the cause of this syndrome. Cervical spine and skull x-rays were normal, as was the electroencephalogram. Psychologic testing indicated a normal personality without evidence of functional disorder.

A right greater superficial petrosal neurectomy was performed on October 2, 1952. The postoperative course was uneventful. Six months after operation there had been no recurrence of his previous distress. He described four or five short-lived attacks of mild pain in the nose, and stated that these were identical to previous premonitory signs of an impending severe attack of pain. Since surgery, however, no such attack had followed any of these infrequent episodes. The patient was greatly pleased with the results of the operation.

Case 3. — A 54 year old white man entered the hospital complaining of intermittent orbitofacial pain limited to the left side which he had had for over 30 years. A typical episode started as an ache in the left neck and left maxillary region, followed by a sudden, severe, knife-like, retrobulbar pain on the left side. This pain was excruciating and it was invariably attended by severe lacrimation and conjunctival injection in the left eye only. On no occasion had the right side ever been involved. When retrobulbar pain appeared, it ordinarily lasted three to five hours and was described as unbearable. Usually attacks occurred at night, ordinarily between 1 a.m. and 3, and awakened him from a sound sleep. For many years the patient had had three or four such attacks each week, but in the recent months prior to hospital admission they occurred every night and prevented him from getting any sleep. He stated that he had received at one time or another "all kinds" of medication without any relief. Several times he had obtained relief through what appeared to be a spontaneous remission lasting three or four weeks, but never any longer than this. Head and neck trauma were denied. At the time of admission, he stated that the pains were so severe that he had been contemplating suicide.

The neurologic and general physical examinations were entirely negative. Histamine injection did not precipitate the described attacks. During several episodes the region about the temporal artery and the supraorbital nerve were blocked with procaine, but these efforts produced no relief. Cervical spine films, skull films, and electroencephalogram were normal. Psychologic test results were interpreted as "situational anxiety in a relatively normal individual."

The left greater superficial petrosal nerve was sectioned on November 28, 1952. Two days following surgery he developed a Bell's palsy on the left which has slowly resolved, leaving only a partial weakness of the left face. When seen five months following operation he stated that occasional mild pain appeared in the left neck and maxillary region, identical to the initial attacks preoperatively. These lasted only two or three minutes and had never progressed to the previous seizures of orbitofacial pain. He had suffered no retrobulbar pain of any kind since surgery.

Case 4. — A 31 year old housewife entered the hospital with the complaint of left orbitofacial pain present over a period of four years. The most severe components of the distress were sharp, cutting pains behind the left eye and in the left supraorbital region. Headaches lasted from two to 48 hours, and were described as so severe that she was unable to even sit up. They were invariably accompanied by pronounced lacrimation and conjunctival injection in the left eye. Attacks occurred without warning, appearing both during the day and at night. When they appeared at night, they awakened her from a sound sleep. Histamine desensitization, alcohol block of the left supraorbital nerve, ergot derivatives, and codeine had failed to provide any relief from this distress. She had been examined by a neuropsychiatrist who recommended that she have psychotherapy.

The general physical and neurologic examinations were entirely normal. The electroencephalogram was normal, as were x-rays of the skull.

A left greater superficial petrosal neurectomy was performed on January 3, 1953. A mild headache appeared on the first and third postoperative days. Following this she began again to have severe hemicrania, limited to the left side of the head. However, questioning re-

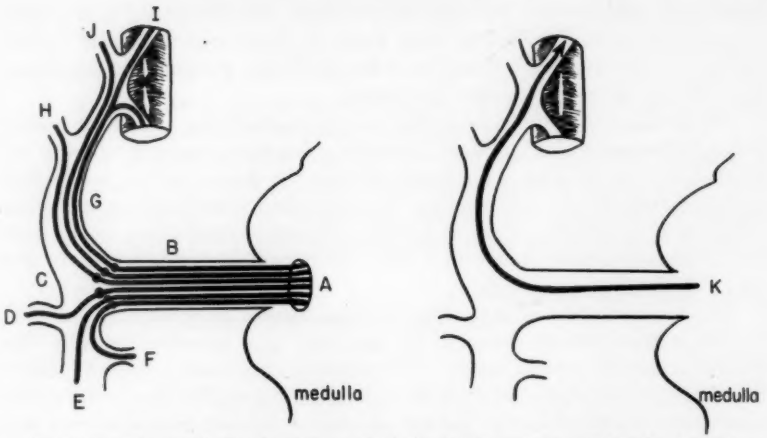

FIG. 2. The efferent and afferent pathways probably involved in greater superficial petrosal neuralgia. *A.* Tractus solitarius. *B.* Nervus intermedius. *C.* Geniculate ganglion. *D.* Afferent fibers from chorda tympani. *E.* Deep sensibility from face. *F.* Cutaneous sensibility from auricular zone of Ramsay Hunt. *G.* Greater superficial petrosal nerve. *H.* Afferent fibers from dura mater. *I.* Afferent fibers from internal carotid. *J.* Vidian nerve. Afferent fibers from sphenopalatine ganglion. *K.* Vasodilator fibers for cerebral blood vessels.

vealed that these attacks were quite different from those occurring prior to surgery. The retrobulbar component of the headache was eliminated entirely, as was the lacrimation and conjunctival injection which previously attended the pain. Moreover, the attacks diminished in frequency to a rather regular cycle of one episode every three days. The pain was described as "burning and aching" of the entire left side of the head. At this time (six weeks postoperatively), psychologic testing was interpreted as showing "severe neurotic conflicts with an hysterical emotional response to these conflicts." Psychotherapy was instituted, and the patient experienced complete cessation of pain.

This case must be classified unequivocally as a surgical failure. Even so, it is interesting that the clinical description of her recurring painful state was essentially identical to that almost totally abolished by surgery in three other individuals. In addition, operation removed the salient features of the described syndrome, yet was followed by a painful state which was described only with great difficulty. It appears possible that a petrosal neuralgia was present, which, when abolished, was replaced by a severe functional disorder.

DISCUSSION

The volume of available clinical and laboratory research data is testimony to the difficulty of the problem encountered in the management of the common problem of headache. Nonetheless, many types of recurrent cephalalgia have been well-defined and yield to specific forms of treatment. Differentiating characteristics which constantly occur in similar complaints would lead one to suspect a constant physiologic disorder as their cause.

In 1932, Chorobski and Penfield[4] reported extensive research into the anatomy and physiology of the greater superficial petrosal nerve. Their findings were that this nerve carried (figure 2): 1) secretory fibers to the lacrimal

gland and nasal mucosa, with vasodilator fibers also distributed to the nasal mucus membrane; 2) afferent fibers from the dura mater, internal carotid artery, and sphenopalatine ganglion to the geniculate ganglion; 3) vasodilator fibers to the ipsilateral cerebral hemisphere.

On the basis of these findings, Gardner[1] postulated that irritation impulses through this nerve could produce headache precipitating vasodilatation in the hemisphere. In addition, pain responses from the dura could be transmitted centrally through the same nerve. Since cerebral vasodilatation has been shown to be productive of headache,[5] this theoretical mechanism would seem to be physiologically sound in explaining painful states localized in the frontal and retrobulbar regions.

The intense nature of lacrimation in these attacks, as repeatedly observed by the authors, would seem to be the only clue strongly indicting the greater superficial petrosal nerve as a necessary anatomical bridge for either the production or appreciation of the painful state described here. The condition labeled by Gardner[1] as "greater superficial petrosal neuralgia" was less specifically delineated than that seen in our small group of cases, although unilateral lacrimation was present in many of the patients in his series.

The group under discussion may be classified by some as a member of the migrainous disorders. Even so, the characteristics, intensity, and location of the pain, and the absence of visual disturbances segregate this disorder from what would be considered classic migraine.

The syndrome of Sluder's neuralgia[6] seems to resemble this complaint more than any described previously. It must be noted that the sphenopalatine ganglion was not blocked in any of these patients. It is conceivable that irritation of the sphenopalatine ganglion could produce head pain through a simple axon reflex. Since such a reflex would necessarily involve the greater superficial petrosal nerve, however, section of that nerve would be expected to abolish headache arising from this source. Likewise, the vidian neuralgia of Vail[7] should respond to petrosal section, since the only part of the geniculate sensory system in this complex is mediated by the greater superficial petrosal nerve. The other petrosal nerves are sensory branches of the glossopharyngeus and innervate the tympanic cavity and mastoid air cells.[8]

No difficulty arose in our patients from the diminution of lacrimation following severance of the greater superficial petrosal nerve. One case of Bell's palsy occurred, but this is resolving slowly.

Three patients in this group have been followed postoperatively for eight, six, and five months, respectively. All of these have been greatly pleased with the effect produced upon their chronic, recurrent headaches. The fourth patient, although a surgical failure, appeared to have had the salient features of the syndrome removed, yet responded poorly to persistent symptoms of more diffuse nature. These latter symptoms disappeared completely with psychotherapy. Further study with long term observation of patients will be

necessary to determine the usefulness of this procedure in the management of recurrent hemicrania.

SUMMARY

1. A syndrome is described which appears to require an anatomic mediator in the form of the greater superficial petrosal nerve.
2. The effects of greater superficial petrosal neurectomy are reported, as observed in a short postoperative period in four patients.
3. Observations to date suggest that this operative procedure is theoretically sound and practical in the management of certain episodic orbitofacial pains.
4. Further clinical studies will be necessary to establish the position of this procedure in the neurosurgical armamentarium.

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In all cases where megrim appears to be in any degree dependent on, or associated with dyspepsia, it will be necessary to enjoin moderate and regular meals, with a simple and nutritious dietary adapted to the digestive capacity and nutritive requirements of the individual, avoiding all such articles of food as are notoriously unwholesome or known to disagree. It is scarcely possible to lay down detailed rules which shall be generally applicable to such cases. Where there is much cardialgia, Lebert recommends a flesh diet; and there are cases, no doubt, where farinaceous and vegetable substances increase acidity and flatulence. Butter and other fatty materials are often shunned by sufferers from megrim in accordance with the precept of Fothergill, and under the notion that they generate bile. This is a doctrine altogether untenable, and I agree with Dr. Buzzard that, as in other neuroses so in sick-headache, oleaginous food, as a general rule, is peculiarly necessary, and much benefit is often derived from cod liver oil. Nevertheless it is only right to add that I have known instances where an abstinence from butter for a time has appeared to diminish the attacks: such are the caprices of this singular disease.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Effect of Mesencephalic Lesions on the Cortical Electroconvulsant Threshold

David A. Freedman, M.D. and John Moossy, M.D.

THAT the sleeping state tends in the human both to increase the incidence of electroencephalographic abnormalities and lower the threshold for convulsions seems well established.[1] This consideration, coupled with the demonstration by Bremer[2] and Lindsley, Bowden, and Magoun[3] among others, that a cerebral state closely resembling sleep in its electrical pattern can be induced by isolating the cerebrum from the brain stem, gave rise to the possibility that such a "cerveau isole" might show alterations in its susceptibility to convulsive activity.

EXPERIMENTAL PROCEDURE

The electroencephalographic electroconvulsant threshold was determined in adult cats. At the time of stimulation the animals were unanesthetized and under artificial respiration with the spinal cord severed at C_1. Electroduragrams were made through six silver ball electrodes placed approximately over the coronal, the lateral, and the post-sylvian sulci. Electric shock was administered between 3 mm. human electroencephalographic electrodes placed on the dura over the lateral extremities of the cruciate sulci. A Medcraft model NC-3 electronarcosis apparatus was used as the source of stimulus.

Following determination of the resting seizure threshold, the brain stem was sectioned at one or more levels in each animal. This was accomplished either by plunging a flat blunt instrument into its substance, or electrolytically using the Horsley-Clarke apparatus. The seizure threshold was redetermined following each brain stem section. Subacute animals were prepared under Nembutal anesthesia 48 hours prior to stimulation. The Jimenez-Castellanos[4] atlas was used as a guide in the Horsley-Clarke experiments.

All brains were fixed in formalin. The stab lesions were examined grossly. Nissl and Weigert sections were made through the electrolytic lesions.

From the department of psychiatry and neurology, Tulane University School of Medicine, New Orleans.

Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 9, 1953.

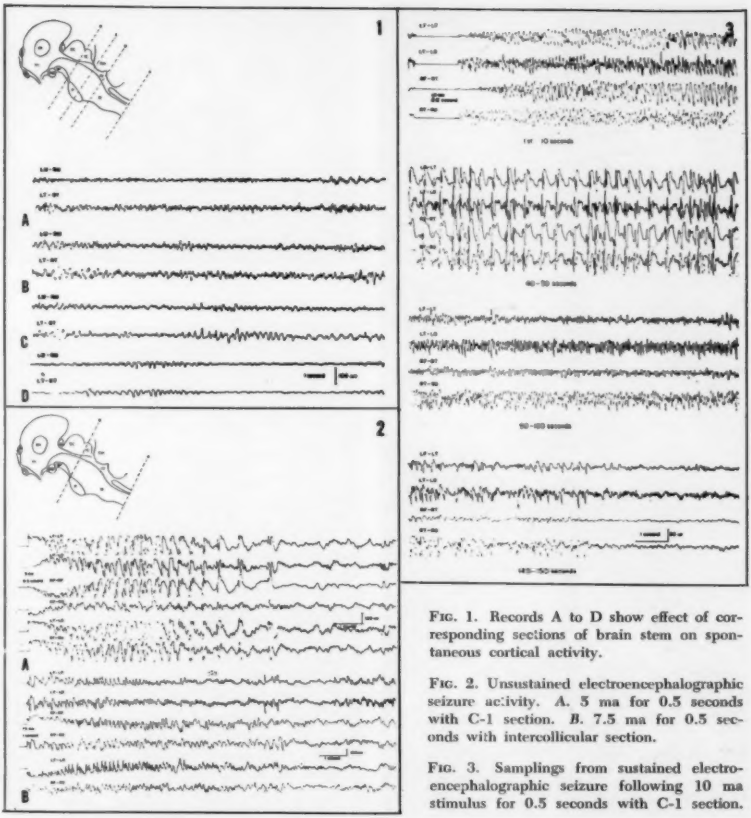


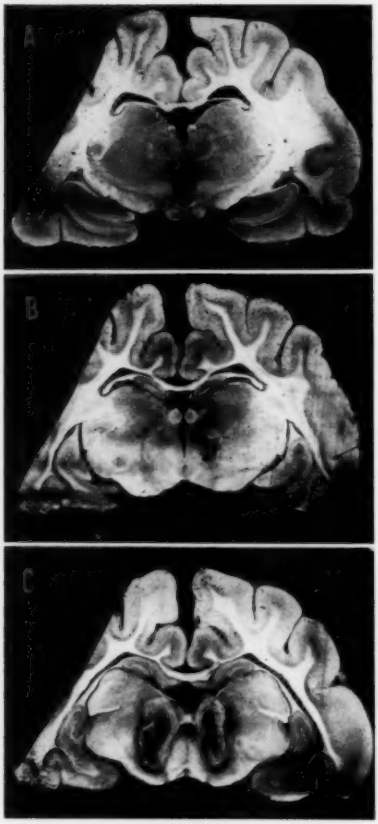
FIG. 1. Records A to D show effect of corresponding sections of brain stem on spontaneous cortical activity.

FIG. 2. Unsustained electroencephalographic seizure activity. *A.* 5 ma for 0.5 seconds with C-1 section. *B.* 7.5 ma for 0.5 seconds with intercollicular section.

FIG. 3. Samplings from sustained electroencephalographic seizure following 10 ma stimulus for 0.5 seconds with C-1 section.

RESULTS

The resting electroencephalograms in these animals were consistent with those originally reported by Lindsley, Bowden, and Magoun[3] (figure 1). The seizure threshold proved to be fairly constant from animal to animal. Under the conditions described and using a stimulus duration of 0.5 seconds, it was possible to obtain some synchronization of the electrodurogram lasting anywhere up to 40 seconds with currents of 5 to 7.5 ma. Such minimal seizures were similar in quality with brain stem sections at all levels. Figure 2 illustrates typical responses of this type. They consist of relatively high voltage activity with some variation in form from experiment to experiment. We have not as yet been able to correlate this variation with the nature of the lesions observed. In contrast to sustained seizures, synchronized activity is not main-



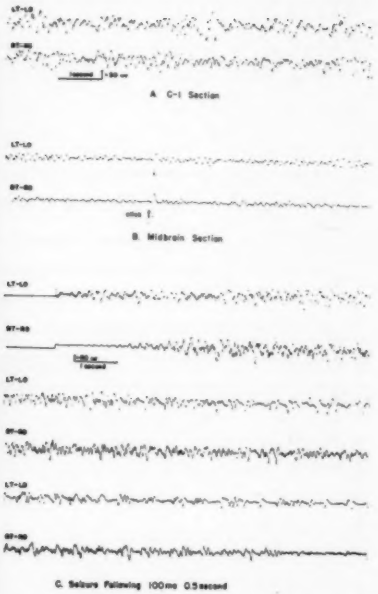


FIG. 4. (*left*) Discrete symmetrical lesions in rostral mesencephalic reticulum. *A*. Intact posterior hypothalamus and mammillary bodies. *B*. Most rostral evidence of electrolytic lesion. *C*. Maximal extent of lesion.

FIG. 5. (*above*) Records from preparation illustrated in figure 4. *A*. Electroencephalogram after C-1 section. *B*. Electroencephalogram following mesencephalic section; note evoked potential. *C*. Response to 100 ma for 0.5 seconds following mesencephalic lesion.

tained. Progressively shorter bursts at longer intervals occur, and within a maximum of 40 seconds the record returns to its prestimulation state.

With lesions caudal to the intercollicular level, stimuli in the range of 10 to 20 ma yield a strikingly different pattern. Such preparations respond with persistent high voltage synchronized activity lasting 60 seconds or more. Figure 3 shows such a response from an animal with section of the spinal cord at C_1.

Following section of the brain stem at or above the intercollicular level it has not been possible to obtain sustained hypersynchronous activity. The brain stem of a lightly anesthetized cat was explored at this level with a stimulating electrode. Using a stimulus of 2 to 5 ma at a frequency of 100 cps, it was found that destruction of relatively few points made further desynchronization of the cortical activity impossible. Figure 4 shows a lesion encom-

Fig. 6.

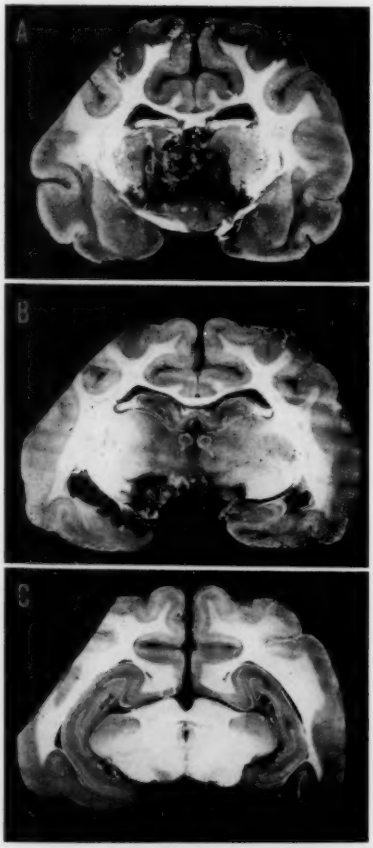


Fig. 8.

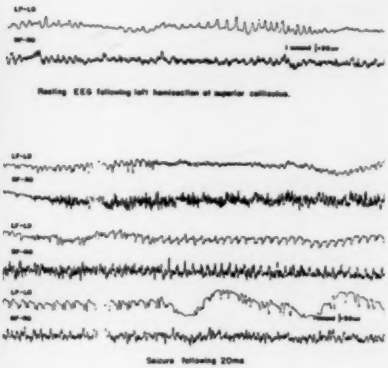


Fig. 7.

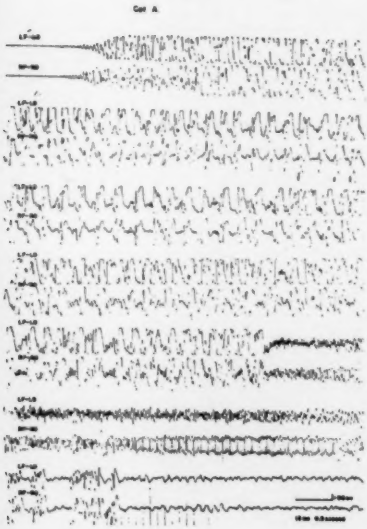


Fig. 9.

FIG. 6. Unilateral electrolytic lesion of rostral mesencephalon.

FIG. 7. Upper record: spontaneous record following lesion in figure 6. Lower record: response to 20 ma for 0.5 seconds.

FIG. 8. *A*. Extensive damage to thalamus. *B*. Destruction of posterior hypothalamus. *C*. Intact mesencephalon.

FIG. 9. Continuous record showing response to 15 ma for 0.5 seconds following lesion shown in figure 8.

passing approximately twice the area destroyed in the foregoing experiment and not involving hypothalamus. This lesion depressed the electroencephalogram in the fashion already described. A stimulus of 100 ma for 0.5 seconds resulted only in an unsustained burst of high voltage synchronized activity (figure 5).

By the expedient of making tracings following each placement of the burning electrode, it was observed that the effect of mesencephalic lesions on cortical activity such as we have described is predominantly, but not wholly, ipsilateral. This observation has been previously reported by Moruzzi and Magoun.[5] A Horsley-Clarke hemisection of the brain stem (figure 6) resulted not only in predominantly homolateral depression of cerebral activity but also in strikingly different seizure patterns in the two hemispheres (figure 7).

Extensive destruction of the thalamus and posterior hypothalamus (figure 8) resulted in no alteration of the threshold for sustained seizure activity (figure 9).

DISCUSSION

From the data presented, it would appear that the integrity of the rostral mesencephalon is essential not only for the maintenance of cortical electrical activity of the form usually associated with the waking state, but also for the occurrence of the sustained hypersynchronous activity associated with major convulsive episodes. It is of interest that Porter[6] has recently demonstrated that the electrical responsivity of the mammillary bodies is similarly dependent on the integrity of the mesencephalic reticulum. Figure 10, taken from Porter's paper,* indicates that a lesion at approximately the same level as those described in the present study obliterates the electrical response of the mammillary body to injected epinephrine.

Granting the validity of the assumption that the physiologic state as well as electroencephalogram of animals with transection of the rostral brain stem is analogous to a normal sleeping state, our findings would appear to be at variance with the clinical observation that sleep often brings out seizure activity. While we are not prepared as yet to resolve this discrepancy, there are considerations which make it seem more apparent than real. In the first place, the frequency with which sedative and anticonvulsant properties are found in the same drug suggests at least that the sedated state is not inherently one which is apt to result in seizure activity. In this regard it may be worth mentioning that every agent of value in the treatment of status epilepticus results in profound sleep. Secondly, we have not noted in our experiments loss in the capacity of the cerebrum to respond with synchronized activity. What we have observed is that our preparations are unable to maintain continuous synchronized activity over a protracted period of time. The possibility remains that some quantitative factor, related anatomically to the amount of reticular substance still in connection with more rostral structures and clinically to the depth of sleep, may resolve this problem.

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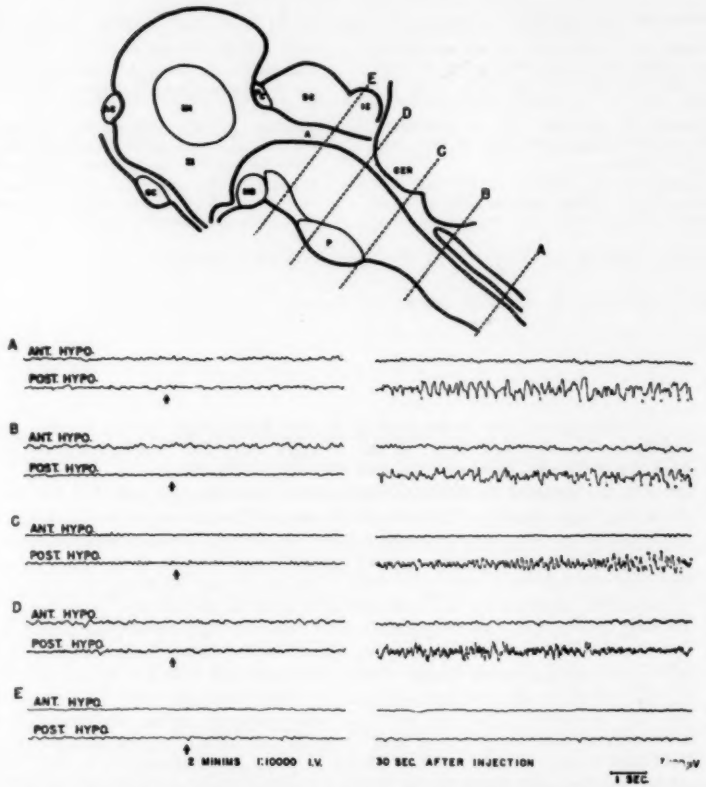

FIG. 10. Records *A* to *D* show marked increase in cat's posterior hypothalamic activity induced by epinephrine after transecting the spinal cord and brain stem at levels shown. Record *E* shows failure of epinephrine to alter hypothalamic activity after transection of midbrain (from Porter[6]).

CONCLUSIONS

In conclusion, we believe we have demonstrated that relatively restricted lesions in the rostral brain stem will limit the capacity of the cerebral cortex to respond to electric shock with sustained seizure activity. This limitation appears to be on the basis of interruption of the connection between the ascending reticular activating formation of Magoun and the cerebral cortex. The relation between these structures appears to be preponderantly but not entirely ipsilateral. Our data, taken in conjunction with Porter's, suggests that, rather than being mediated by the hypothalamus, the influence of the midbrain reticular substance is equally as relevant to hypothalamic as it is to cortical activity.

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A discharge of the motor centres in one hemisphere causes a convulsion on the opposite side. If this is slight, only the muscles of unilateral use may be involved. In such convulsion the muscles of bilateral use (as the muscles of ordinary respiration) may escape, probably because the very equality of representation in the two hemispheres of the brain involves a less absolute representation in either. If the discharge is greater in degree, it involves, besides the unilateral muscles of the opposite side, the bilateral muscles of both sides, in proportion to the degree of functional association. The muscles of the thorax are affected equally. The leg on the same side may be affected, but in a slighter degree than the other. The arm usually escapes. Hughlings Jackson believes that when the spasm spreads to the whole of the second side the discharge is still limited to the one hemisphere. In some cases this may be true. But the character of the convulsion, in other cases in which the spasm has involved first one side and then the other, seems to suggest strongly that there is an extension of the discharge from one hemisphere to the other. In the early stage of the fit we have deviation of the head and eyes to the side first affected, and as the spasm is lessening on this side there is a similar deviation of head and eyes to the side secondarily affected, and the convulsion on this side passes through the same stages as on the other, on which it has often ceased when it is at its height on the second side. The corpus callosum is known to connect the convolutions of the two hemispheres, and Brown-Séquard has lately demonstrated by experiment that through its fibres the motor centres of the cortex may be called into action.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Blood in the Subarachnoid Space

A Clinical Evaluation of Its Occurrence in 190 Consecutive Cases

Morton Nathanson, M.D., Alvin L. Robins, M.D. and Martin A. Green, M.D.

In the literature concerning subarachnoid bleeding, a great deal of attention has been directed to the dramatic picture of the so-called spontaneous subarachnoid hemorrhage, usually occurring in adults between the ages of 20 and 50 years and presumably due to rupture of a congenital aneurysm.[1–6] As a result, physicians not directly associated with the fields of neurology and neurosurgery have gained the impression that rupture of a congenital aneurysm is the most common cause of spontaneous subarachnoid bleeding. While the evidence for this statement may be strong, it refers only to a part of the entity of blood in the subarachnoid space.

The sources of error in determining the etiologic incidence in this condition are great. The percentage of patients in whom angiography is indicated and performed still is rather small. The number of negative and positive angiograms varies greatly. The number of deaths and the percentage of postmortem examinations reflects only a fraction of the total number of cases. Statistics obtained from hospital records are limited for the most part to those actually diagnosed as subarachnoid hemorrhage. There are many patients who, during their course in the hospital, have been noted to have blood in the subarachnoid space as a manifestation of other disorders, but frequently no indication of this is made on the discharge classification.

The purpose of this investigation has been to evaluate clinically the occurrence of blood in the subarachnoid space found in consecutive cases admitted to a large general hospital. Because it was not possible to be definite about the etiology in a great many of these patients, they were classified clinically and not pathologically.

From the departments of neurology and psychiatry, New York University College of Medicine, and the third neurologic and psychiatric divisions of Bellevue Hospital, New York City.

Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 9, 1953.

One hundred and ninety patients with blood in the subarachnoid space who were admitted to the neurologic, medical, surgical, and psychiatric wards of Bellevue Hospital during an 18 month period were studied. For each patient at least two spinal punctures were performed and the usual criteria for establishing true subarachnoid bleeding were followed. History, general physical, and neurologic examinations were performed on all the subjects and follow-up observations were noted. Another communication will deal with these findings in more detail.

RESULTS

The greatest number of patients (39 cases) in whom spontaneous bleeding into the subarachnoid space occurred was in the hypertensive-arteriosclerotic group (table 1). Here the often described picture of a sudden, severe headache followed by signs of meningeal irritation was relatively rare. Only eight patients in this group had such an acute onset of headache. The rest began with hemiparesis (21 cases) or with a picture of confusion and disorientation but no localizing signs (ten cases). All patients in this group had evidence by history or direct measurement of moderate to severe hypertension. When

TABLE 1

190 CONSECUTIVE CASES WITH BLOOD IN THE SUBARACHNOID SPACE

	Age range	*No.*
A. Traumatic		116
B. Nontraumatic		74
1. Hypertensive-arteriosclerotic	51–79	39
2. Normotensive young and middle-aged adults	23–48	16
3. Unclassified	42–58	11
4. Neoplasms		5
5. Others (blood dyscrasia, 1; infections, 2)		3

first examined only 18 of the 39 patients had meningeal signs (table 2). However, nine of the remaining 21 patients subsequently (two to three days later) showed signs of meningeal irritation. One postmortem examination was obtained in this group out of 15 deaths (table 3). The brain, in this instance, showed a large cerebral hematoma with extension into the ventricles and subarachnoid space. A second case was partially verified by an operation when an intracerebral clot was aspirated.

In the next group, that of the young and middle-aged adults without evidence of hypertension (16 patients), all but two showed the typical picture of spontaneous subarachnoid hemorrhage, consisting of the sudden onset of severe headache followed almost immediately by all the signs and symptoms of meningeal irritation. This group was considered to have rupture of a congenital aneurysm as the basis for the bleeding. There was no history of hypertension in any of these patients; previous attacks had occurred in four. There were four deaths and three postmortem examinations. All

TABLE 2

NUMBER OF PATIENTS WITH MENINGEAL SIGNS IN THE VARIOUS GROUPS OF THE ENTIRE SERIES

	No.	*Initial examination*	*24–72 hours later*
A. Traumatic	116	64	81
B. Nontraumatic	74	42	53
1. Arteriosclerotic-hypertensive	39	18	27
2. Normotensive young and middle-aged adults	16	14	15
3. Unclassified	11	5	7
4. Neoplasms	5	2	2
5. Others (blood dyscrasia, 1; infection, 2)	3	2	2

showed ruptured aneurysms. Nine angiograms were performed in this group, and three showed evidence of an aneurysm (table 3).

The 11 unclassified cases were either younger adults with severe hypertension (four patients) or persons aged 50 to 57 with no evidence of hypertension by history or examination (seven patients). Of the 11 subjects in this group, six had sudden onset of severe headache with meningeal signs, while in five the onset was vague, the clinical picture for the most part being that of an organic mental syndrome without meningeal signs (table 2). If the cases of this unclassified group were to be added to the group presumably having ruptured congenital aneurysms, the total would still fall short of being the most common clinical picture where blood in the subarachnoid space was encountered.

TABLE 3

A. Number of deaths and postmortem examinations of the nontraumatic group (74 cases)		
Deaths – 28		Autopsies – 10
Findings:	Neoplasms	5
	Aneurysms	3
	Intracerebral hematoma with leakage into subarachnoid space	1
	Tuberculous meningitis	1
B. Angiograms – Total 9		
3 positive for aneurysm		

The five patients with cerebral neoplasm presented an entirely different clinical picture from those in the groups already mentioned. The history usually showed fluctuations of mental and focal neurologic deficits for weeks or months. The reason for admission was a definite worsening of symptoms, usually in the form of organic mental changes, convulsions, or aphasia. All cases proved to have malignant neoplasms at postmortem examination, with hemorrhage into the abnormal tissue and leakage into the subarachnoid space or ventricles (table 3).

As would be expected from the nature of the population studied, the traumatic group was much larger than the spontaneous cases. Of particular interest is the fact that a great number of patients with bleeding due to trauma did not show any of the signs of meningeal irritation. In fact, it was not unusual to find such patients walking about the ward without discomfort.

COMMENTS AND SUMMARY

It is evident from this series that if the information gained by autopsy and angiography were used, a distorted concept of the etiology of blood in the subarachnoid space would be obtained. It is true that a much larger consecutive series with the equivalent percentage of autopsies and angiograms may prove to be more significant, but still the present limitations of angiography and the unpredictable number of deaths and postmortem examinations are formidable barriers.

The data presented merely focus attention on the most common clinical condition where blood in the subarachnoid space is found, namely vascular disorders associated with hypertension and arteriosclerosis, rather than the familiar and often reported syndrome of spontaneous subarachnoid hemorrhage due to a ruptured congenital aneurysm.

The lack of meningeal signs[7,8] in many of these patients, especially those in the hypertensive-arteriosclerotic and traumatic groups, should emphasize the point that the absence of meningeal signs does not eliminate the possibility of bleeding into the subarachnoid space.

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Cerebral Arteriovenous Aneurysms

William H. Druckemiller, M.D. and*
Malcolm B. Carpenter, M.D.

Until recently the diagnosis, localization, and treatment of cerebral arteriovenous aneurysms presented almost insurmountable difficulties. Cushing and Bailey[1] in their monograph woefully expressed the problem as follows: "To extirpate one of these aneurysmal angiomas in its active state would be unthinkable and so far as we are aware there is no report in the literature of the attempt having been made." Dandy[2] considered most of these aneurysms inoperable, but recommended decompression when pressure symptoms were present. Olivecrona has been credited[3] with the first successful removal of an anteriovenous aneurysm of the brain. The aneurysm in this case occurred in the posterior fossa. Moniz'[4,5] contribution of cerebral angiography has made possible accurate preoperative diagnosis and localization of these vascular malformations, thus enabling the neurosurgeon, aided by recent advances, to attack the lesions directly.

Statistical data regarding the frequency of cerebral arteriovenous aneurysm are meager, and the incidence of these lesions cannot be judged from cases reported in the literature. Dandy collected only 22 case reports from the literature and admitted that some of these were unconfirmed. The frequency of these lesions among series of verified brain tumors may be found in table 1. Olivecrona and Riives[6] have pointed out that cerebral arteriovenous malformations occur approximately twice as often in males as in females. Available data concerning the sexual distribution of these lesions, as recorded in the literature, are summarized in table 2.

PATHOLOGY

Comprehension of the pathology of cerebral arteriovenous aneurysms requires an embryologic approach, for the responsible developmental disturbances occur in the early embryo. The adult system of cerebral arteries and veins is derived from a general capillary network which undergoes extensive metamorphosis by the elaboration of certain channels, the formation of temporary arteries and veins, and the comparative and total obliteration of other

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The opinions expressed here are those of the authors and do not constitute the official policies or views of the Bureau of Medicine and Surgery of the U. S. Navy.

TABLE 1
REPORTED INCIDENCE OF CEREBRAL ARTERIOVENOUS ANEURYSMS

Authors	*Number of cases of arteriovenous aneurysms*	*Among this number of brain tumors*
Cushing and Baily[1]	9	1,522
Dandy[2]	8	600
Bergstrand, Olivecrona and Tonnis[10]	18	941
Olivecrona and Riives[6]	60	3,206

vessels, presumably in accordance with contemporary developmental requirements.[7] For reasons not yet fully understood, incomplete differentiation and development sometimes occur resulting in retention of abnormal nests of blood vessels, with direct anastomosis of arteries and veins. This developmental defect causes "arterialization" of venous channels[2] with concomitant shunting of highly oxygenated blood, thus resulting in impaired cerebral circulation distal to the anastomosis. The dramatic, impressive nature of these pulsating, vermoid tangles of vessels as seen at operation is completely lacking at postmortem examination.[1] Histologic study of surgical specimens is not reported frequently, probably because the gross pathology is characteristic. Cushing and Bailey's study of surgical specimens revealed unequal development of the various coats of the vascular wall, imperfect formation of the media, "nodular" overgrowth of the intima, and faulty development of the internal elastic lamina. Hyaline, fatty, and calcific degeneration were observed in various portions of the vessel wall, though such findings were not constant. The adventitia was found to vary greatly in thickness and seemed to bear no relation to the caliber of the vessel. Most authors agree that these vascular malformations seem to occur with greatest frequency in the distribution of the

TABLE 2
SEXUAL DISTRIBUTION AMONG 146 PATIENTS WITH CEREBRAL ARTERIOVENOUS ANEURYSMS

Authors	*Date*	*Male*	*Female*
Cushing and Bailey[1]	1928	7	2
Dandy[2]	1928	8	0
Bergstrand, Olivecrona and Tonnis[10]	1936	15	7
Ray[10]	1941	4	2
Pilcher[17]	1946	1	2
Wechsler and Gross[18]	1948	2	4
Trupp and Sachs[14]	1948	14	6
Olivecrona and Riives[6]	1948	29	13
Norlén[3]	1949	6	4
Jaeger[15]	1950	1	1
Bassett[11]	1951	12	6
	Total	99	47

middle cerebral artery, but they may be found at other sites, including the vessels of the cerebellum and brain stem.

SYMPTOMS

The onset of symptoms may occur at any age, but most patients are relatively free of symptoms and/or signs until the second or third decade of life. Precisely why these lesions which probably existed from birth should not provoke symptoms earlier is unknown. Convulsive seizures, often focal in type, are the most common initial symptom. Such seizures usually increase in frequency and severity with time and are often refractory to anticonvulsant therapy. Petit mal and psychomotor seizures[2] have also been reported, though they are uncommon. Spontaneous subarachnoid hemorrhage is probably the second most common finding with its attendant symptoms of severe continuing headache and meningeal irritation. Olivecrona and Riives[6] stated that subarachnoid hemorrhage initiated symptomatology in about 20 per cent of their cases. When subarachnoid hemorrhage occurs, it often is not as severe as that associated with the so-called "berry" aneurysm. The exact incidence of fatal initial hemorrhage is unknown. The sudden onset of paresis, sensory disturbances, aphasia, and visual defects is common, though highly variable in extent and form; such symptoms may at first be transitory but often become permanent later. Intracerebral hemorrhage is the usual cause of such symptoms. Psychic disturbances and mental degradation[8] have been observed in cases of long-standing cerebral arteriovenous aneurysms. Progressive atrophy of the brain, particularly the cerebral cortex, due to short-circuiting of blood flow through the aneurysm has been postulated as the cause of these symptoms. Headache[9] is common and often not unlike that associated with severe migraine.

DIAGNOSIS

Prior to the development of cerebral arteriography, the diagnosis of cerebral arteriovenous aneurysm was usually made on a history of focal seizures, spontaneous subarachnoid hemorrhage, the presence of a bruit, and roentgen evidence of floccular intracranial calcification. Although these findings are characteristic, they are not found in all cases. A bruit, said to be pathognomonic of the condition, is not common, and is frequently missed because of failure to auscultate the cranium. It is rarely elicited when the blood supply of the aneurysm comes entirely from the internal carotid artery.[6] Intracranial calcification likewise is unusual, occurring primarily in older patients. Pneumoencephalography may be helpful in localizing the aneurysm, particularly when coexistent with an intracerebral hematoma, but distortion and shift of the ventricular system in the absence of intracerebral hemorrhage are usually minimal. Ventriculograms revealed significant defects in five of the six cases reported by Ray [10] and in four of the 18 cases described by Bassett.[11] Olivecrona and Riives[6] performed air studies in most of their cases; the most frequent observation was cerebral atrophy. The malformation was large enough

in some cases to cause "dislocation" of the ventricular system, which was always slight but suggestive of an expanding lesion. They regarded ventricular "dislocation" associated with varying degrees of cerebral atrophy as strong evidence of cerebral arteriovenous aneurysm.

In spite of Dandy's reluctance to use cerebral angiography,[12] this technic has come to occupy a unique and valuable position in the neurosurgical armamentarium. It is obvious that diagnosis and localization of cerebral arteriovenous aneurysms are most readily made by arteriography. This technic affords an opportunity to study preoperatively both arterial and venous phases of the cerebral circulation, particularly when serial roentgenograms are made with the Fairchild apparatus. Thorough preoperative evaluation of the nature, extent, and exact localization of the arteriovenous aneurysm probably has contributed more to successful surgical treatment than any other technical advance.

TREATMENT

As recently as 1928 the foremost neurosurgeons considered these arteriovenous lesions to be hopeless and recommended palliative procedures, such as roentgen therapy and surgical decompression. No proof is available that radiation causes significant shrinkage of these malformations, but pathologic data indicate that non-irradiated lesions in time increase in size and cause progression of symptomatology. Ligation of the carotid vessels (either internal, internal and external, or common) has been performed as a therapeutic measure by Dandy,[2] Ray,[10] Wechsler and Gross,[13] Trupp and Sachs,[14] Jaeger,[15] and Bassett.[11] Wechsler and Gross concluded that this procedure was beneficial and commented: "As far as followed no patient with a carotid ligation had subsequent spontaneous subarachnoid hemorrhage." In one case reported by Jaeger[15] a fatal subarachnoid hemorrhage occurred following carotid ligation. Olivecrona and Riives[6] have become convinced that ligation of the carotid artery is "more dangerous than excision of the malformation," because permanent hemiplegia may follow the procedure as it did in two of their six cases. Attempts to coagulate the arteriovenous anomalies by electrocautery as reported by Trupp and Sachs[14] resulted in a 20 per cent operative mortality and increased neurologic deficits in many instances. Another 20 per cent of their patients succumbed within two years of surgery from causes seemingly related to their aneurysms. These authors admitted "stroking" the vessels with electrocautery was not without hazard, and in some instances brisk and uncontrollable hemorrhage resulted. Bassett's combined electrocoagulation and ligation of "feeding vessels" produced variable and unpredictable results.[11]

Surgical extirpation of cerebral arteriovenous aneurysms, when possible, is the treatment of choice. Successful removal of these lesions has been reported by Penfield and Erickson,[16] Pilcher,[17] Olivecrona and Riives,[6] Dott,[18] Norlén,[3] and Bassett.[11] Norlén has stated that the risks of permanent and severe physical and mental incapacitation or fatal hemorrhage in this condition, if untreated, is greater than the surgical risk of removal. In the only large series of cases,[6]

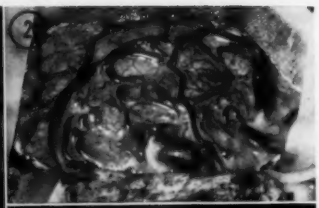
operative mortality in 43 cases was 9.3 per cent. Recent advances in anesthesia (for example, controlled hypotensive states) have facilitated removal of lesions to such an extent that downward revision of the mortality statistics may be expected. Increasing success in extirpation of these lesions is due primarily to improved methods for diagnosing, localizing, and studying the particular features of the aneurysm in the individual patient, as afforded by cerebral angiography. In patients sustaining intracerebral hemorrhage with resulting hemiplegia, aphasia, mental deterioration, or other significant neurologic deficit, extirpation of the vascular malformation is not likely to be followed by full restoration of function. Under these circumstances excision of the inciting lesion is often facilitated and can be accomplished without increasing the nature or extent of the existing disability, because the lesion usually lies in tissue already devitalized and non-functional. Once the lesion is removed entirely, the progressive nature of the condition is interrupted abruptly. It is obvious that the best surgical results can be expected in those cases with the smallest amount of irreversible neural damage. Therefore early operation should be encouraged. The question of the effect of surgical removal of an aneurysm of this type upon convulsions cannot be answered fully, although Olivecrona and Riives[6] found a significant reduction in the number of seizures occurring postoperatively.

Postoperative cerebral angiography provides important data concerning restoration of cerebral circulation and is the only means of determining whether the aneurysm has been completely extirpated. Norlén[3] performed postoperative angiograms on nine of his ten cases, and noted a reduction in the caliber and tortuosity of numerous vessels formerly feeding into the aneurysm. Within a period of two or three weeks the vascular pattern usually appeared normal, with increased visualization of small vessels peripheral to the vascular anomaly. This has been interpreted as indicating improvement of cerebral circulation.

CASE REPORTS

Case 1.—As a result of falling and turning his right ankle in the summer of 1951, a 19 year old man was examined by a medical officer who found moderate weakness and atrophy in the peripheral musculature of the right lower extremity. Symptomatic treatment effected only slight improvement. In January 1952 he again fell while walking and was hospitalized. Examination disclosed hypalgesia over the right leg, in addition to the weakness and atrophy noted earlier. The deep reflexes were said to have been increased in the right lower extremity and unsustained ankle clonus was described. A few days after admission the patient had a focal seizure which began in the right hand. The following day he was transferred to the U.S. Naval Hospital at St. Albans.

On admission the patient was alert, well oriented, and complained of sensory changes in the right leg described as a "dead feeling." He stated that weakness in the right leg had been progressive for about seven months. Some impairment of skilled movements in the right arm was also noted and was reflected in a degradation of handwriting and drawing. On questioning he admitted minimal but increasing difficulty of verbal expression. General physical examination was within normal limits. Neurologic examination disclosed: 1) hypalgesia in the second division of the trigeminal nerve on the right, 2) fine nystagmoid movements on extreme lateral gaze to both the right and left, 3) impairment of



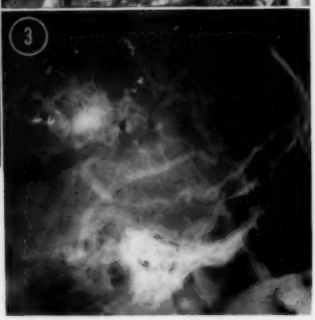


FIG. 1. Left carotid arteriogram demonstrating arteriovenous aneurysm. Note the unusually large caliber of the anterior and middle cerebral arteries and the poor visualization of the smaller branches of these vessels. The linear markings are artifacts.

FIG. 2. Gross appearance of the arteriovenous aneurysm at operation.

FIG. 3. Demonstration of the arteriovenous aneurysm following the first attempted surgical extirpation. Figures 1 to 3 illustrate case 1.

rapid successive movements in the right upper extremity, 4) minimal weakness in the muscles of the right upper extremity and moderately severe weakness and atrophy of the right quadriceps, hamstring, gastrocnemius, and anterior tibial musculature, and 5) impairment of pain, tactile, position, and vibratory sense in the peripheral portions of the right lower limb. The deep reflexes were approximately equal in threshold, force, maturation, reflexogenous zones, and spread bilaterally, but the amplitude was greater in the lower limbs and a brisk quality was noted on the right. Roentgenograms of the skull were within normal limits, as were the electroencephalogram and the tests of the visual fields and acuity.

A left cerebral arteriogram done on January 28 revealed a large collection of radiopaque material in the parietal region (figure 1). This was observed during both arterial and venous phases, yet seemed most prominent during the arterial phase. The left anterior and middle cerebral arteries appeared greatly enlarged and tortuous. On the basis of this study a tentative diagnosis of cerebrovascular malformation (arteriovenous type) was made. On February 4 a left parietal craniotomy was performed, revealing a large parasagittal angiomatous mass (figure 2); venous structures within this malformation were noted to have arterial pulsations and a bright red color. An attempt to ligate the arterial supply of the malformation was made, but considerable hemorrhage was encountered during the procedure and it became necessary to ligate the anterior cerebral artery. The operation was terminated because resection of the aneurysm did not seem feasible. Postoperatively the patient exhibited aphasia, moderate right sided paresis with spasticity, and impairment of sensation on the right side of the body. On the second postoperative day there was papilledema of approximately two diopters bilaterally, and the patient was unable to look to the right. On the tenth postoperative day the spastic paresis began to diminish and the expressive aphasia appeared to be resolving. From this time on continued improvement was observed. Toward the end of February the patient became fully ambulatory, but slight residual aphasia and a right spastic hemiparesis remained. A left

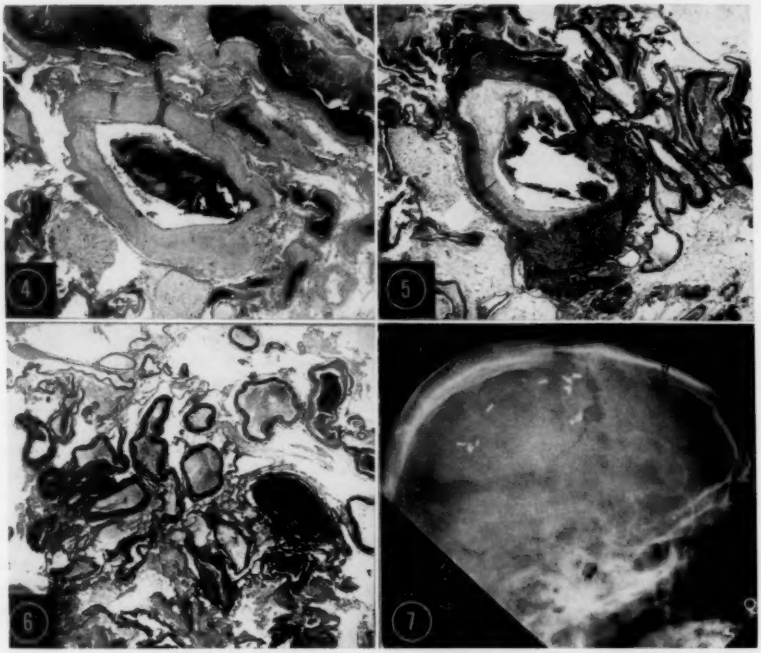


FIG. 4. Photomicrograph of part of the arteriovenous aneurysm extirpated showing principally three larger vascular channels and numerous smaller vessels of different caliber. The central vessel contains a partially organized mural thrombus. Note the marked variations in the thickness of the intima and media as well as the imperfect formation of both. The two large vessels above show intimal proliferation and defective formation of the intima and media. Closer examination of most of the smaller vessels revealed similar histologic features. Two islands of glia (predominantly astrocytes) can be seen below the large central vessel.

FIG. 5. Photomicrograph demonstrating the same characteristics as seen in figure 4. Collagenous and elastic fibers of the media are clearly visualized and defects in distribution are apparent. Fragments of a mural thrombus are seen in the central vessel.

FIG. 6. Photomicrograph of a section taken from another part of the aneurysm showing the wide variations in the caliber of the vessels, as well as defects in the vessel coats.

FIG. 7. Postoperative arteriogram after extirpation of aneurysm at the second operation. Figures 4 to 7 illustrate case 1.

cerebral arteriogram on March 24 revealed some reduction in the size of the arteriovenous aneurysm (figure 3). Reexamination in May 1952 disclosed no significant change in neurologic status, although the aphasia seemed less. A systolic bruit was elicited over the left eyelid. Sensation was impaired to pin prick and cotton wool over the entire right lower extremity.

A second craniotomy was performed on May 14 under controlled hypotensive anesthesia (sodium Pentothal supplemented by curare and hexamethonium),* at which time

*During operation 400 mg. of hexamethonium chloride was administered in divided doses; 40 mg. given initially was supplemented by 20 mg. doses as needed. Blood pressure was maintained evenly at about 70/50 mm. Hg. Although bleeding was copious at times, it was always easily controlled. Following extirpation of the angiomatous malformation, no additional hexamethonium was given; the systolic blood pressure rose to 90 mm. and remained at that level for six hours. At the end of this period the blood pressure spontaneously returned to the preoperative level, 140/90 mm.

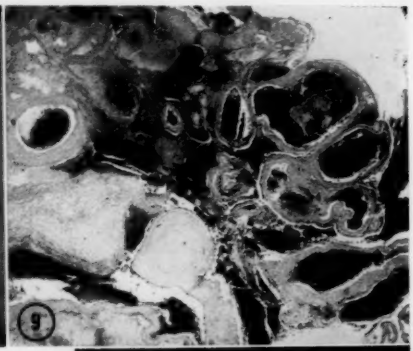
the entire vascular anomaly was extirpated with minimal trauma to surrounding tissue (figures 4, 5, 6). The postoperative course was smooth and not marked by additional neurologic deficit. On June 4 a postoperative left cerebral arteriogram (figure 7) disclosed that the entire arteriovenous aneurysm had been removed and the vascular pattern had returned to normal. After an appropriate convalescence the patient was discharged.

Case 2.—A 22 year old, right-handed man developed a sudden severe generalized headache associated with difficulty in speaking and "numbness" in the left hand and arm on May 14, 1952. Although the patient became slightly disoriented, he did not lose consciousness. He was admitted to a hospital where examination was said to have revealed moderate paresis of the left side of the body and hemihypalgesia. A lumbar spinal puncture disclosed grossly bloody cerebrospinal fluid. An attempted cerebral arteriogram resulted in filling of the external carotid artery only. A pneumoencephalogram was interpreted as being within normal limits. After a few weeks the left hemiparesis subsided leaving residual weakness in the upper extremity and a dysarthric type of speech. On August 3 the patient was transferred to St. Albans Hospital for further treatment. On admission he appeared well oriented and alert, but demonstrated difficulty in pronouncing multisyllabic words. The general physical examination was within normal limits; neurologic examination revealed slight weakness in the lower face on the left and some weakness in the left upper extremity. Skilled movements were poorly performed with the left hand and tests of coordination revealed slight dyssynergia. Deep reflexes were found to be increased in the left upper extremity, while the abdominal and cremasteric reflexes were normal. The left plantar response was equivocally extensor. Sensation was impaired to pin prick over the left half of the face and in the left arm and hand. Roentgenograms of the skull were perfectly normal; an electroencephalogram and analysis of the spinal fluid were unremarkable. Visual acuity was 20/20 bilaterally, and no abnormality was found on visual field studies. A battery of psychologic tests (Wechsler-Bellevue, Bender Motor Gestalt, and Rorschach) showed the patient to be of average intelligence, with some impairment of accuracy in learning new associations involving visual-motor coordination.

On August 26 a right cerebral arteriogram was done which revealed an arteriovenous malformation in the distribution of the middle cerebral artery measuring approximately 4 x 5 cm. (figure 8). Trolard's vein appeared dilated and unusually large in caliber. A second electroencephalogram was reported to be within normal limits. On September 24 a right frontoparietal osteoplastic flap was turned; upon opening the dura, the vein of Trolard was of unusually large caliber, appeared bright red, and pulsated vigorously. Controlled hypotension was initiated with hexamethonium.* (blood pressure maintained at about 70/50 mm. Hg) as a transcortical incision was made anterior to Trolard's vein and carried to a depth of about 1.5 cm. The angiomatous malformation was found at this site, surrounded by old blood pigment and necrotic tissue. After three large feeders from the middle cerebral artery were isolated and ligated, the entire vascular anomaly was extirpated with ease (figure 9). Posteriorly the malformation was found to be adherent to the ependyma of the right lateral ventricle. Following resection of the lesion, the vein of Trolard appeared blue and ceased to pulsate. Postoperatively the patient was oriented, alert, and exhibited no increased paresis or speech impairment. The only increased neurologic deficit was a moderate degradation of ability to interpret skin writing in the palm of the left hand. A cerebral angiogram done after surgery (figure 10) disclosed that the aneurysm had been removed completely and that the vascular pattern had returned to normal.

Case 3.—A 34 year old woman in the eighth lunar month of an uneventful pregnancy developed sudden stiffness of the neck and severe bitemporal headache while talking on

*A total of 70 mg. of hexamethonium chloride was given at operation. The blood pressure was returned to its preoperative level of 120/70 mm. immediately after removal of the lesion by employing an intravenous Neosynephrine drip.



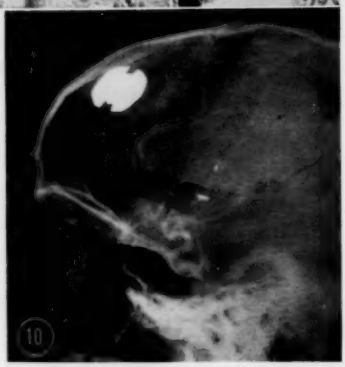


FIG. 8. Arteriovenous aneurysm as seen in preoperative arteriogram.

FIG. 9. Photomicrograph of a section of the aneurysm showing histologic characteristics similar to those described in case 1. The medium sized vessel in the lower central area has been obliterated by hyalinization of the proliferating intima.

FIG. 10. Postoperative cerebral arteriogram demonstrating complete extirpation of the aneurysm. Figures 8 to 10 illustrate case 2.

the telephone September 21, 1952. A few minutes later she became nauseated, vomited, and lost consciousness. Several hours later she was found on the floor in a semiconscious state by her husband who immediately took her to a general hospital. The findings on examination at that institution are not known, except that lumbar spinal puncture revealed a grossly bloody cerebrospinal fluid. No history of prior head trauma or seizures could be elicited. On admission to St. Albans Hospital several hours later, the patient was found in a state of severely depressed consciousness and was unable to relate a medical history. Aside from marked mental torpidity, moderate nuchal stiffness, equivocal extensor toe responses, and moderately hyperactive, but equal deep reflexes, examination was unremarkable. Fetal heart sounds were of good quality and the rate was 140 per minute. During the next few days no change was noted in the patient's condition, although the headache became less severe. Two weeks after admission her conscious state appeared greatly improved and she could answer questions; moderate preservation and retrograde amnesia continued. Bilateral percutaneous carotid arteriograms were technically poor, but disclosed an apparent cerebral vascular abnormality on the right; on the left, filling was confined to the external carotid and its branches. One week later bilateral cerebral arteriograms were performed after surgical exposure of the carotid vessels. The vascular pattern was entirely normal on the left, but on the right the Sylvian vessels appeared distinctly and markedly displaced dorsally. A radio-opaque mass was seen in the posterior inferior temporoparietal region (figure 11). Examination on October 20 when the patient was more cooperative revealed slight weakness of the lower facial musculature on the left, weakness in the left upper

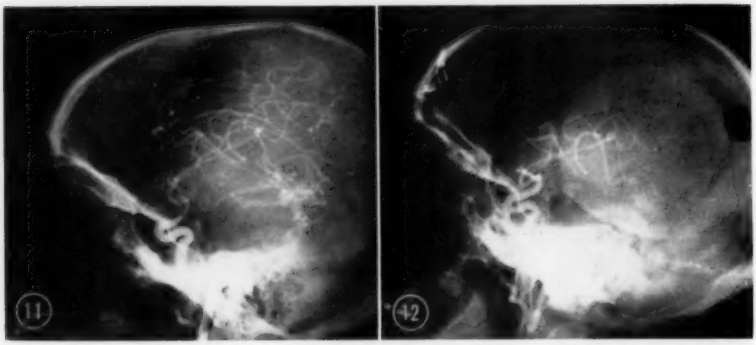


FIG. 11. Preoperative cerebral arteriogram demonstrating the arteriovenous aneurysm in case 3.
FIG. 12. Postoperative arteriogram revealing subtotal removal of the arteriovenous aneurysm.

extremity, and a left superior homonymous quadrantic field defect. No sensory deficit or extinction phenomenon could be found. On October 22 a right parietal craniotomy was performed; the dura appeared bluish and when incised about 15 cc. of blood-stained fluid escaped from the subdural space. When the dura was turned down a well organized membrane of a subdural hematoma was present. The posterior inferior temporoparietal cortex contained rust-stained pigment and was adherent to the dura. Cannulation of the brain at this point revealed a cavity approximately 3 x 6 cm. filled with old blood. A transcortical incision was made into the hematoma; an estimated 40 to 50 gm. of solid clot were removed. Inspection of the cavity revealed a mass of abnormal vessels on the posterior and superior walls which was removed after ligation of feeding arteries. During the procedure the patient's blood pressure remained about 100/60 mm. Hg and no attempt to reduce it further was made. Postoperatively the neurologic status was unaltered, though the patient was somewhat drowsy and disoriented for a few days. The fetal heart rate was still 140 per minute and the sounds were of good quality. Follow-up cerebral arteriography (figure 12) disclosed a small unextirpated portion of the lesion. Because the expected date of confinement was imminent, reoperation was not feasible. The tentative plan was to repeat cerebral angiography six months postpartum and re-evaluate the findings. Three weeks after surgery the patient was delivered of a normal full term infant by low forceps. The postpartum course was uneventful.

DISCUSSION

Increasing experience in the treatment of cerebral arteriovenous aneurysms has demonstrated clearly that total extirpation of the lesion is the only effective procedure. Unless the lesion is removed the threat of subsequent hemorrhage, either subarachnoid or intracerebral, remains. Since all cerebral arteriovenous aneurysms are not resectable, the surgeon must select those cases which, on the basis of angiographic studies or exploration, appear amenable to surgery. Obviously numerous factors influence the ultimate decision, among which are the size and location of the malformation. Size of the lesion alone need not necessarily be a deterrent to surgery, for some of the larger lesions, particularly if superficial, can be extirpated without significant parasurgical trauma. Except in some cases of massive arteriovenous aneurysm, the risk

of leaving the lesion alone is greater than the risk of surgery. Aneurysms located in the left cerebral hemisphere carry a risk of greater neurologic deficit whether or not an attempt at removal is made. It should be emphasized that little improvement can be expected by removing vascular malformation from a patient who has already sustained severe and repeated hemorrhages culminating in incapacitating hemiplegia, mental deterioration, or other irreversible neurologic symptoms. If surgical extirpation of the lesion is to be attempted, it should be done early to avoid the risks of hemorrhage and brain atrophy. Once intracerebral hemorrhage has occurred, the aneurysm may still be excised, often without great difficulty, for removal of the clot often affords excellent exposure of the malformation and feeding vessels. Since specific tissue deficits are usually irreversible, complete restoration of functions destroyed by the hemorrhage cannot be expected.

It is not surprising that carotid ligation has proved useless and in many instances hazardous in the treatment of these aneurysms, since further reduction of pulse pressure and blood flow in the cerebral vascular tree probably only increases the ischemia in those portions of the brain supplied by vessels distal to the site of the arteriovenous shunt. Many authors have mentioned precautionary exposure of the internal carotid artery prior to attempted extirpation of an arteriovenous aneurysm. This has been done to provide some control of local hemorrhage, should it occur. Increasing experience has shown[3] that this additional procedure is not necessary as a routine. In the first case presented here this precaution was taken, but in succeeding cases it was not done.

Controlled hypotension, a relatively recent adjunct to surgery, has expanded the scope and facility of neurosurgery. Probably many cerebral arteriovenous aneurysms could not be extirpated without an aid of this type. It is of course desirable to return the blood pressure to its normal level as soon as the vascular anomaly has been excised. Case 1 is an example of a vascular malformation which probably could not have been resected in a normotensive state.

SUMMARY

A brief review of the literature of cerebral arteriovenous aneurysms and the various forms of treatment has been presented. Three cases in which this type of vascular malformation was removed surgically are reported in detail. Postoperative cerebral arteriography verified the completeness of the extirpations and demonstrated restitution of normal cerebrovascular patterns.

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Although most attacks of epilepsy consist of both tonic and clonic spasm, in some fits there is but one form of spasm, tonic or clonic. As a rule, those which consist only of tonic spasm are generally fits of slight severity. A patient falls unconscious, is rigid for a few moments, and then is better. Occasionally more severe attacks consist only of tonic spasm, as the case of a boy of whose fits the following is a description. His head was first turned to the right; then his arms became extended and rigid, the right being more abducted from the body than the left. Both elbow-joints were then flexed, and his fingers were flexed in the interosseal position. In a few moments the spasm ceased, lasting a little longer in the hands than elsewhere. There was no clonic spasm. He had also more severe attacks, consisting only of tonic spasm, but in them the arms were raised above the head; there was foaming at the mouth; and the tongue was bitten. These severe tonic fits (the "tetanoid epilepsy" of Pritchard) are not common.

In some patients who present both forms of spasm, the tonic stage is very long, and the clonic stage is very short. For instance, a boy, in one attack which was witnessed, put his head a little back, his arms were put forward, and he became rigid. The trunk was twisted a little to the right, and the face was drawn towards the right side. This continued for about thirty seconds; there was then slight general clonic spasm for two or three seconds, and the attack was over.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Hemangioendotheliomatous Meningioma Simulating Cerebral Arteriosclerosis

T. Lehoczky, M.D.

IN PATIENTS over 50 it is often difficult to distinguish between a brain tumor and a case of cerebral arteriosclerosis. This problem has been prominent in the earlier neurologic literature as well as more recently. Wechsler[1] even considered it as occasionally offering insurmountable difficulties. Hastings[2] assumed the presence of vascular lesions in 19 of 25 cases of brain tumor. Pennybacker[3] stated that in 68 cases of brain tumor, all in patients over 60, the diagnosis may have been generally late, because the general symptoms of brain pressure appear rather late or diseases of blood vessels in the brain (hypertension, cerebral arteriosclerosis) often imitate the symptoms of tumor.

In this presentation the diagnostic difficulties are illustrated by a case in which it was impossible to distinguish with certainty between a brain tumor and cerebral arteriosclerosis, either by clinical symptomatology or the macroscopic appearance of the brain. The tumorous character of the disease could only be decided by histologic examination.

CASE REPORT

A 52 year old male patient suffered a spasmodic seizure with unconsciousness, which reappeared twice successively after four years. At that time all clinical examinations were negative except for mild arteriosclerosis. Therefore the possibility of a brain tumor was left open. The epileptic attacks were explained as a result of cerebral arteriosclerosis, and the patient was treated accordingly. Two years later, in the sixth year of the disease, Jacksonian attacks lasting 40 to 60 seconds appeared over a period of six hours. There was conjugate deviation of the left side and faciobrachial convulsions on that side. Thereafter the following symptoms remained permanently: difference of the pupils (the left more dilated than the right), central facial paresis of minor degree with Oppenheim and marked Barré symptoms on the right, and ataxic gait with closed eyes. Because brain tumor was suspected another detailed examination was performed, including x-ray of the skull, examination of ocular fundi, and spinal fluid studies, with negative results. During the following six years the patient was without any complaints and showed no symptoms of general brain pressure. During this time he had three or four epileptic seizures which were, according to the report of his family, of a generalized character like those experienced at the beginning of the disease. Between seizures the patient took anti-epileptic drugs regularly and felt well.

From the department of neurology, István-Hospital, Budapest, Hungary.

In the thirteenth year after the first symptoms, that is, at the age of 65, profound psychic changes gradually took place: considerable forgetfulness, gradual neglect of his duties, emotional incontinence, increasing irritability and harshness of manner towards his wife, gradually growing indifference. He lay in bed or sat in an armchair all day, and was repeatedly incontinent of urine and feces.

The patient was treated in our department during the two and a half months prior to his death. He showed a central facial paresis on the left, Mayer reflexes bilaterally increased, right patellar reflex increased, and Oppenheim and Gordon symptoms on the left. There was a very strongly pronounced perioral reflex. Laboratory data were as follows: blood pressure 165/110, blood sugar 137 mg. per cent, hyperchromic anemia of minor degree, sedimentation rate of 30-64, later 80-115.

The mental picture was that of grave organic dementia: intense lack of initiative, indifference, poor concentration of attention, memory concerning new impressions considerably diminished, lack of interest, occasional euphoria, tendency to childish jocularity, incontinence.

Course of disease: Increasing dementia; decubiti, first at both heels, later at the sacrum; acute polyarthritis; later bilateral femoral thrombophlebitis. At the same time there was confabulation (the patient thought he was a warship); there were illusions, confusion of persons, later total apathy. These symptoms appeared alternately during the whole time of treatment in the hospital. The polyarthritis improved; later the temperature rose to 38° C., and infiltration of the lower lobe of the right lung appeared. In the last two weeks he did not reply to questions, took a minimum of food, grew worse rapidly, and died.

Autopsy: Chronic myocarditis with coronary arteriosclerosis; fibrinous pleuritis; pulmonary infarct; renal infarct; cholelithiasis; sacral and calcaneal decubiti.

The gyri of the brain's surface were somewhat smooth, with no striking appearance of brain pressure. The ventricular system was normal, with no signs of dilatation. There was moderate cerebral arteriosclerosis; the internal carotid arteries on both sides were gaping and rigid-walled, but without considerable thickening. Small plaques were seen at the starting point of the medial and anterior cerebral arteries and in the lower part of the basilar artery.

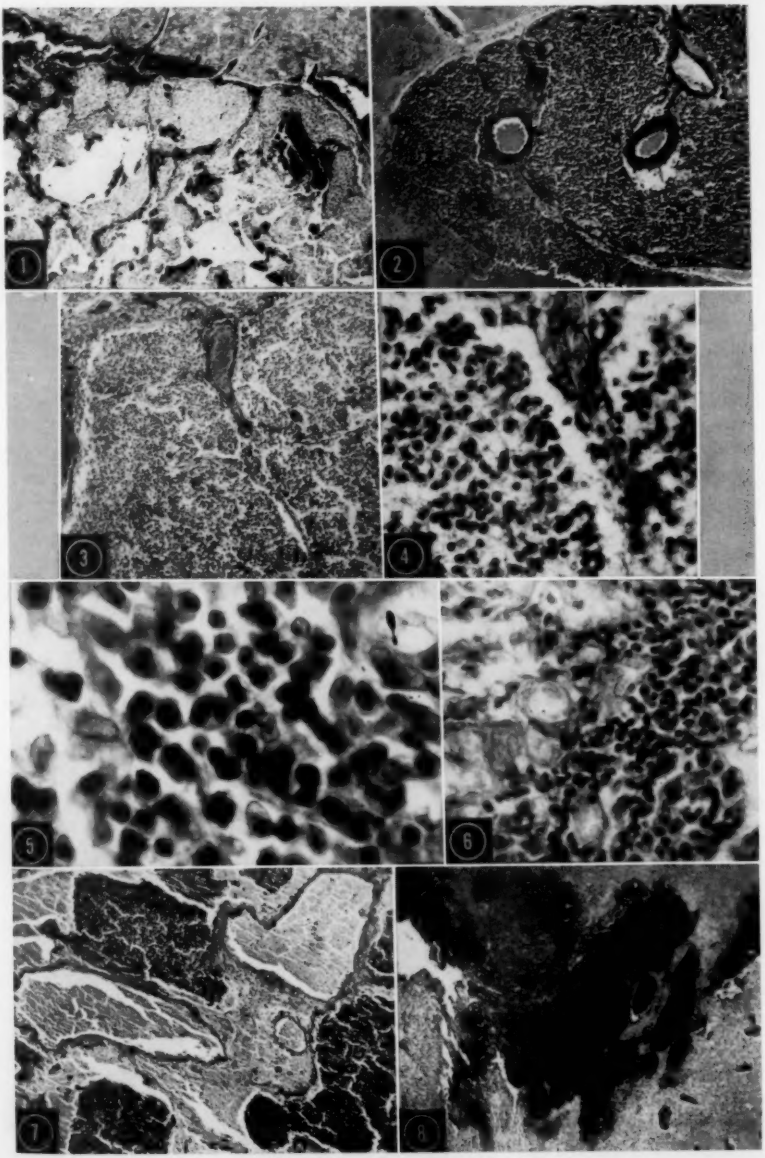
Both frontal poles were softened and contained hemorrhagic (tumorous?) areas reaching the cortical substance; on the left there was a smooth-walled cyst similar to that found in an old softening. In the white substance of both frontal lobes were peculiar channels infiltrated by blood. These contained small softened cysts which did not reach the surface. In the white substance of the left frontal lobe two almost parallel hemorrhagic channels of 1 cm. were seen; on the right the white substance was broadened without any pathologic alterations.

At the level of the genu of the corpus callosum the white substance of the right frontal lobe was broadened; on the left small hemorrhagic areas were seen in the white substance. Posterior to this level no alterations were found, either in the cerebrum or in the cerebellum.

Histologic examination: Tumorous tissue was found in the meninges; this widened the sulci and penetrated, like tumorous islands, into the intact cortical substance (figures 1 and 2). The tumor was in general sharply separated from the parenchyma, but infiltrations could be observed which were in some places direct, in others following the sheath of the blood vessels. At these points small tumor centers arose in the nerve substance. In some places the tumor extended over the cortex in broad zones and infiltrated it in its whole width.

The cells of the tumor formed definite, small, lobe-like clusters, at the edge of which, but in the substance of the tumor itself as well, vessel networks were seen in abundance (figures 3 and 4). The cells of the tumor were large and angular; their plasma could be stained with eosin. The nuclei were of different size with no division of the nuclei (figure 5).

Here and there the tumor had a distinctly angiomatous character, showing a microangioma-like picture. Between the newly formed small blood vessels, the cells of the tumor were very rich in plasma and were ranged in rows, almost like epitheloid cells (figure 6).



See text for explanation of figures.

In other places greatly widened small, thin-walled veins, suggestive of real cavernous changes, were seen. Between these the tumor tissue appeared as an island (figure 7). In the interior of the tumor were smaller and larger hemorrhages, which partly infiltrated the substance of the nerve tissue (figure 8).

Histologically, according to the terminology of Globus, the tumor was a pial (vascular) meningioma.

COMMENT

This case is a striking example of the difficulties which may arise in differentiating between brain tumor and cerebral arteriosclerosis.

1. The disease began with a late epileptic fit of generalized character. According to our own data,[4] epileptiform attacks occur in general in 41.1 per cent of brain tumors; Penfield and Erickson[5] observed this in 53 per cent of frontal tumors; Moreau in 52 per cent. According to experience, the frontal and temporal tumors are the most epileptogenic ones. Therefore, we did our utmost to exclude the existence of a tumor, but as the clinical neurologic and laboratory data (spinal fluid, ocular fundi, x-ray of the skull) were all negative and the patient had general arteriosclerosis, we decided on the latter.

In the sixth year of the disease the possibility of a tumor became more evident, since at that time the patient had a series of Jacksonian attacks each lasting 40 to 60 seconds within six hours. Our supposition was increased by the fact that the following organic symptoms became permanent: anisocoria, central facial paresis, marked Oppenheim and Barré symptoms on the right, and ataxic gait. Spinal fluid, ocular fundi, and skull x-ray examinations were repeated, but they were all negative. The patient did not consent to an encephalographic examination. The Jacksonian attacks did not return, but seizures of general type occurred once or twice every year.

2. Symptoms of general brain pressure were absent till the end. The absence of papilledema and nausea can be explained by the exceedingly slow development of the tumor over 13 years. Chavany and Woringer[6] have studied the absence of headaches in frontal tumors. On the basis of examination of 137 frontal tumors, they concluded that those patients do not suffer from headaches in whom a characteristically frontal psychic symptom group is developed. They explained this contrast by establishing "spontaneous anatomic or functional lobotomy." Our case confirms their opinion, since the bilateral lesion of the frontal lobe appeared surprisingly similar to the macroscopic picture of prefrontal lobotomy or leucotomy.

3. The psychic symptoms were, over a period of 12 years, identical with the usual symptoms of arteriosclerosis: difficult concentration, absentmindedness, weariness, irritability, later ever-increasing indifference. In the last year grave organic dementia developed: change of personality, intellectual confusion, disorientation, later followed by illusion, change of personality, apathy.

Thus the disease corresponded to a bilateral frontal lesion, which was explained by repeated arteriosclerotic softening or small bleedings.

4. Of the general somatic symptoms, the very important cardiorenal condition (moderately increased blood pressure of 170 to 180 mm. Hg, not too rigid

peripheral arteries, no signs of decompensation) gave little enlightenment. Of course, the fact that a tumorous patient can also suffer from arteriosclerosis was taken into consideration. Certainly a slowly growing tumor could disturb the conditions of circulation in the brain to such a degree that the vascular symptoms might come more to the foreground. This double etiology may render the diagnosis even more difficult.[7]

The present case demonstrates unusually sharply the diagnostic difficulties. Not only the course of disease, but its final development and even the macroscopic picture of the brain rendered probable an arteriosclerotic cerebral lesion, and not a tumor of the brain.

The clinical explanation of this could be summed up in the fact that the brain tumor, during its 13 year development, did not produce any reliable symptoms suggesting a tumor. It is probable that, even if the patient had consented to a ventriculographic or angiographic examination, we should not have been able to identify the tumorous character of the disease. Since the tumor occupied the white substance of the poles of both frontal lobes, that is, the part before the frontal horns, we should not have been able to find any essential deviation in the encephalogram. This is proved by the brain section in which the ventricular system appeared quite normal. The same can be said of the arteriogram, as the branches of both the pericallosal and the callosomarginal arteries were lying posterior to the tumor and would have shown a normal picture or an unimportant small deviation. It must be taken into account that, even had the tumor been verified, it is doubtful whether this would have led to some practical result. Pennybacker's[3] opinion seems to be valid that if a tumor in an aged patient is growing slowly and gives no trouble, operation is needless.

The pathologic explanation is provided by the histologic structure of the tumor, which is namely a pial (vascular) meningioma. This particular and rare sort of tumor, pressing on the brain substance over a large area from outside, from the direction of the pia, causes a very slow atrophy in it (figures 1 and 2). In certain places the cells of the tumor penetrated directly or along the sheaths of the blood vessels into the cortex, but this process never reached such a degree as is seen in a malignant tumor.

This tumor, which originated from the meninges, grew very slowly, expanding gradually over both frontal lobes. It was characterized by slow development and a misleading psychic syndrome. It is possible that the rapid deterioration observed during the last months was caused by repeated older and newer hemorrhages into the substance of the tumor (figure 8). The histologic picture of the tumor deserves special attention.

The classification of meningiomas has been a frequent subject in the newer neurologic literature. Globus stated in 1937 that his was the thirteenth classification since Cruveilhier. This was followed by the classifications of Lichtenstein-Ettleson, Cushing-Eisenhardt, Masson, Roussy-Cornil, Oberling, Hortega, Benedek-Juba, Bertrand, Guillaume, and Olteanu. These 20 classifications prove

that the histologic picture of meningioma is manifold and offers many possibilities with regard to the histologic structure as well as its origin.

The survey was facilitated by the work of Bertrand, Guillaume, and Olteanu, integrating the former literary classifications. In their opinion five basic types can be postulated: 1) indifferential or mesenchymatous, 2) omniforme, 3) fibroblastic, 4) arachnoideal, 5) pial types. They enumerated the synonyms in every group, which makes the survey much easier. They emphasized the frequent transitionary and atypical forms, in consequence of which the diagnosis of meningioma has, in many cases, just as fine nuances as that of gliomas.

Surveying the newer classifications we see that the evaluation of psammomatous or fibroblastic, osteochondroblastic, melanomatous, lipomatous, and sarcomatous groups is uniform. There is no discordance on this point. Difficulties arise in the recognizing and ranging of the mesenchymatous, angioblastic, meningotheliomous tumors, respectively, following the terminology of Globus: the indifferentiated, the omniforme or primitive arachnoid leptomeningioma, and the pial (vascular) types. Doubtlessly our case belongs to this latter group which is difficult to classify; we have not observed fibroblasts, psammoma bodies, bone formations, or sarcomatous degeneration.

In accordance with the classification of Bertrand, Guillaume, and Olteanu, the tumor in question is a mixed form of three types: I. indifferential or mesenchymatous, IV. arachnoid meningioma, and V. pial hemangioma. The greater part is built of types I and V, so it can be considered as a mixed or transitory form of these two.

According to the classification of Bailey and Bucy our patient's tumor can be ranged into the mesenchymatous and angioblastic groups.

According to the terminology of Globus the tumor is a transition between meningioma indifferentiale or mesenchymatous meningioma, and meningioma onmiforme or primitive meningioma. From the former the "foam cells" and "liquefaction" and from the latter the bone and collagenous elements are lacking. In some areas capillaries have developed in abundance, at some places even cavernomas and sinusoids can be noted, which indicates that meningioma piale (vascular meningioma) is also present.

Summing up we may say that the tumor belongs to the rare, indifferential, mesenchymatous or meningotheliomatous group of meningioma, in which hemangiomatous parts are also to be found.

In conclusion, a diffuse pial (vascular) meningioma, growing slowly for many years, not infiltrating the brain substance at all or only very slightly, and causing no symptoms of brain pressure, can be very easily confused with cerebral arteriosclerosis.

SUMMARY

A 65 year old man had suffered a generalized epileptiform attack 13 years previously. In the sixth year after the initial seizure, he had a series of Jacksonian attacks, then marked pyramidal symptoms, and an increasing organic dementia in the last year of illness.

In the white substance of both frontal lobes a hemorrhagic, softened tumor reached the pole. Histologically this was a pial (vascular) meningioma; its hemangioendotheliomatous subtype was found.

The histologic picture of this rare sort of tumor makes the lack of brain pressure symptoms and the confusion with cerebral arteriosclerosis understandable.

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Another provocative of the seizures which is frequently met with in megrim is the over-stimulation of the sensorium from any occupation or engagement which involves a prolonged exercise of any of the senses, or a more general excitement and strain of the sensorial faculties. A day of sight-seeing in town, a long railway journey, a public spectacle or military review, are pretty sure to be followed in some individuals by one or more attacks. Evening entertainments of almost every kind are particularly trying; the concert, the playhouse, the evening assembly, and even the church, present a combination of impressions,—of sights and sounds, of glaring lights and impure air,—together with a certain element of emotional excitement, which are extremely prejudicial, and should be shunned as far as possible by the sufferers from megrim, who must content themselves with simpler forms of social enjoyment.

Where the occupation is such as considerably to tax the sight, and the seizures appear to be in any way connected with the use of the eyes, we should inquire carefully into the state of vision, and if we detect the presence of myopia, hypermetropia, or other faulty condition, we should endeavor to correct it as far as possible by suitable glasses and rest.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Prenderol: A New Drug Used With Retarders in Petit Mal Epilepsy

M. A. Perlstein, M.D.

Until the advent of Tridione and Paradione there were no reliable drugs that could be used effectively in the management of petit mal. Recently reports have appeared on the effectiveness of other drugs, such as Phenurone[1] and phenyl succinimide.[2] Most drugs employed in the management of petit mal epilepsy may produce sufficient unpleasant or toxic side effects to preclude their use even when they are clinically effective. Therefore, any new drug that might prove advantageous in petit mal epilepsy, especially if it were relatively innocuous, would be extremely welcome. This paper reports experience with what promises to be such a drug.

Prenderol chemically is 2,2-diethyl-1,3-propanediol; structurally it is an analogue of Tolserol (3-ortho-toloxy-1,2-propanediol). Originally synthesized for possible use as a muscle relaxant, the drug was found relatively non-toxic to animals[3,4] and to men,[5] with a high anticonvulsant action against electroshock in the cat and against Metrazol in the mouse. Prenderol is readily soluble in water and is rapidly absorbed as well as eliminated from the gastrointestinal tract. Administered in large doses, it causes slowing of the normal electroencephalogram and may even produce spikes.

Prenderol is said to act on the multisynaptic mechanisms in the spinal cord and midbrain, blocking the facilitory impulses coming to the muscles.[6] When given to human beings, the drug acts for a very short period. Clinical experiences with the drug indicate that it begins to function within 15 to 30 minutes after ingestion, but because of its rapid rate of excretion its effectiveness may only last for 15 to 60 minutes thereafter. Consequently, in order to increase its effectiveness, it is necessary either to administer it at one to two hour intervals or to employ agents that will retard its rate of absorption and excretion. Unless this is done, one may receive the false impression that the drug

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is entirely ineffective. With the use of a retarding agent, the span of effectiveness produced by a single dose of Prenderol may be increased to between three and five hours. Unfortunately, no practical chemical method for assaying blood or urine levels of the drug is available, so that only clinical observation can be relief upon to determine the prolonged therapeutic effect produced by retarding agents.

The following case report illustrates the effect of retarders on the prolongation of pharmacologic action:

An 18 year old white male with severe congenital athetosis, marked tension, and dystonia was given 2 gm. of Prenderol* orally to achieve relaxation. The patient experienced definite relaxation beginning 20 minutes after ingestion and lasting for a period of 15 minutes. After addition of retarders in the form of 1 ounce of 32 per cent cream or 1 teaspoonful of PVP** (polyvinylpyrrolidone) powder per individual dose, the period of relaxation was prolonged to between three and five hours. Continuous relaxation was then achieved by having the patient take the medication, together with the retarding agent, every four hours.

DOSAGE

Prenderol was supplied in the form of 0.25 gm. and 0.5 gm. scored tablets. The dose employed varied from 0.5 gm. to 2.5 gm. four times a day, the average dose in the case of children being 1.0 gm. four times a day. Dosages below 0.5 gm. proved ineffective, while those above 2.5 gm. occasionally caused nausea or dizziness; doses above 2.5 gm. did not generally increase the efficacy of the drug. Dosages of Prenderol up to 140 mg. per pound of body weight per day were well tolerated by some patients. As a rule the drug was prescribed at intervals of four hours. The general plan for utilizing Prenderol was to prescribe it for four days without a retarder, then to add a retarder, usually whipping cream, to determine whether the effectiveness of the drug was enhanced. In the beginning a retarding agent, consisting of whipping cream (32 per cent fat) in amounts of one ounce, was administered with each dose of Prenderol. The dose was chosen empirically; in many instances one-half to one-third of this amount proved sufficient to enhance the pharmacologic effect of Prenderol. When whipping cream was refused by patients or not available, one-half tablespoonful of either olive oil, corn oil, or cod liver oil was employed. Occasionally a teaspoonful of butter or a small scoop of ice cream was found equally efficacious. Many patients added appreciable weight under this regime. When limitation of the caloric intake was desirable, a non-caloric retarder was employed. PVP (polyvinylpyrrolidone) powder in one-half to one teaspoonful dosages was also found effective as a retarder when added to food or dissolved in a small amount of water or palatable liquid; on the other hand, carbomethyl cellulose in similar amounts proved somewhat less satisfactory than PVP. Paraminobenzoic acid, glycerin, and other retarding or

*Prenderol for this study was supplied by Dr. H. S. Newcomer of E. R. Squibb & Sons, New York, N. Y.

**Polyvinylpyrrolidone (PVP) powder was supplied through the courtesy of Dr. Richard K. Richards of the Abbott Laboratories, North Chicago, Illinois.

blocking agents were tried in some instances, but experience with them has been inconclusive.

To test the efficacy of Prenderol dispensed in an oily menstruum, capsules were provided containing 0.25 gm. of the drug in about 5 minims of oil. The size of capsules containing double this amount of medication were too large for pediatric use. Although the effective time of action of the drug was occasionally lengthened, the capsules of Prenderol in oil were not found to be practical because too many had to be given (approximately 16 daily), because many children could not swallow capsules, and primarily because additional retarder had to be given in most instances anyway to achieve the maximum benefit from the drug.

SOURCE AND TYPE OF POPULATION

The patients under study were seen in private practice, at the Children's Neurology Clinic of the Cook County Hospital, Chicago, and at the St. John's Home and Hospital for Crippled Children, Springfield, Illinois. Virtually all the children had been observed for prolonged periods of time and had been under treatment with other drugs, usually without appreciable benefit. A

TABLE 1
EFFECT OF PRENDEROL ON NON-SEIZURE PATIENTS

	No.	Marked Benefit
Athetoids	13	4
Spastics	12	0
Sydenham's chorea	2	0
Myasthenia gravis	1	0
Behavior disturbance	5	0
Total	33	4

total of 103 patients were observed. Of these, 33 with varied neurologic conditions were studied to determine the relaxing or tension-relieving effects of Prenderol (table 1). In addition, 70 patients with seizures of various types were studied for the anti-epileptic properties of Prenderol. Since 18 of this group had two types of seizures of sufficient frequency to judge the possible benefits of drug therapy, table 2 shows a total of 88 seizure instances in these 70 patients. The age of the patients under treatment ranged from two to 42 years, with the average being about ten years. Of the 103 patients, there were 53 males and 50 females, with 81 white persons and 22 negroes. Age, sex, and race did not apparently affect the response to the drug. For the most part, the epileptic patients observed were those in whom other drugs had been used ineffectually to control seizures. Thus, patients with petit mal generally had taken Tridione, Paradione, Phenurone, and other drugs, while those with

other types of seizures had been treated with drugs of both the hydantoin and barbiturate groups. Clinical improvement in the status of seizures, once it occurred, usually appeared within 12 to 24 hours following institution of medication. Benefits were generally sustained; at the time of this report, spells have been controlled for periods ranging from one to 22 months. It is interesting to note that in some patients who responded favorably, cessation of medication was not always followed by reinstitution of seizures. Clinical response was considered beneficial only when improvement was sustained by patients for at least one month. In some instances, relapses in the number of seizures occurred in spite of continuation of Prenderol medication, but to no greater degree than that observed after the use of other drugs.

RESULTS

Muscle relaxing effect: In assaying the clinical benefits derived from the use of muscle relaxants, one must be aware that psychologic factors may be more potent than pharmacologic ones in causing relaxation.[7] For a drug to be considered effective, it is necessary to use placebos as controls. In this study only those patients evincing relaxation after medication, but not in the case of

TABLE 2
EFFECT OF PRENDEROL ON PATIENTS WITH SEIZURES

	No.	Benefit ****	**	Worse
Grand mal	22	1	1	6
Petit mal	48	22	8	3
Myoclonic	8	2	0	0
Focal	6	0	0	0
Psychomotor	4	0	0	0
Total	88	25	9	9

****—marked improvement—over 90% reduction in spells.
**—partial improvement—50-90% reduction in spells.
There were 70 patients, 18 of them with combined spells, to make a total of 88 instances.

placebos, were considered to have been benefited. Past experience with Tolserol had indicated that most benefits reported following use of this drug were probably of a psychologic nature. In view of this experience, the evaluation of Prenderol as a relaxing agent was done with considerable caution.

In the group of 33 non-seizure patients only four were benefited. These were from a group of 13 athetoid cerebral palsied patients (table 1). It was in this group of patients, characterized by the case reported above, that it was possible to determine the length of time of action exerted by Prenderol, with and without the use of a retarder. Why the drug proved more effective

TABLE 3
EFFECT OF PRENDEROL ON PATIENTS WITH IDIOPATHIC AND ORGANIC SEIZURES

	Idiopathic		Organic	
	No.	****	No.	****
Grand mal	11	1	11	0
Petit mal	28	18	20	4
Myoclonic*	0	0	8	2
Focal	0	0	6	0
Psychomotor	3	0	1	0
Total	42	19	46	6

****—marked benefit.

in the case of extrapyramidal lesions than in spastics with pyramidal tract disease is not clear; it may possibly be due to the fact that the drug has a predilection for action on midbrain or basal nuclear areas. The observation that petit mal spells were more benefited than grand mal seizures may lend credence to the assumption that petit mal spells originate from the midbrain rather than from the cortex.[8] A similar action of Tridione has also been noted.[9] The children with behavior disturbances represented true emotional problems and had no evidence of organic brain disease. None of the five children in this group was benefited, nor was the single patient with myasthenia gravis nor the two with Sydenham's chorea.

Results in seizure cases: In judging the effectiveness of Prenderol in the case of seizures, four categories were employed: 1) marked improvement (****), to indicate 90 per cent or more reduction in seizures; 2) partial improvement (**), to indicate 50 per cent to 90 per cent reduction in seizures; 3) no improvement, to indicate less than 50 per cent improvement; and 4) aggravation of symptoms. Of a total of 88 instances of seizures, 34 were appreciably benefited and nine were aggravated (table 2). Patients with petit mal seizures were benefited most, 30 of 48 persons showing demonstrable benefit, with but three being aggravated. On the other hand, only two of 22 patients with grand mal showed benefit, while six were aggravated. In two of eight patients with myoclonic* spells marked benefit was noted. Further analysis of the data, by separating them into a group with evidence of organic brain damage and a so-called idiopathic group, demonstrates that idiopathic petit mal is helped more than any other condition. In table 3 only patients with marked benefit were included; and of 28 idiopathic petit mal patients, 18 were helped while only four of 20 persons with petit mal incident to organic brain

*By myoclonic spells are meant momentary, rapid jerky flexor movements of the arms and often the head. Various names, such as "lightning" grand mal spells, petit mal myoclonus, and other terms have also been used to describe this condition. It is seen more frequently in infants in association with organic brain disease.

TABLE 4
EFFECT OF RETARDERS

	Total	Petit Mal–Benefited ****	**	0	Grand Mal Worse
Prenderol alone	30	3	13	14	1
Addition of retarders	30	22	8	0	6

disease were benefited. This is in keeping with the general observation that drugs are more effective in idiopathic forms of epilepsy than in those with organic brain disease.

Effect of retarders: The striking effect produced by the addition of a retarder to Prenderol is summarized in table 4. Of 30 patients with petit mal seizures who were benefited, only three had marked benefit, while 14 were not helped when the drug was prescribed alone. On the other hand, after the addition of a retarding agent, maximum benefits were detected in 22 patients. Of the 18 patients with petit mal seizures who derived no benefit from Prenderol, even after the addition of a retarder, 16 were associated with organic brain disease. It is also interesting to note that the effect of Prenderol in precipitating grand mal seizures is enhanced by the addition of the retarder. Since most of the patients with both petit mal and grand mal were receiving anticonvulsants in addition to Prenderol, a question arises whether the effect of the retarder on Prenderol precipitated the grand mal seizures, or whether the retarder's possible effect in inhibiting the action of phenobarbital, Dilantin, or other anticonvulsant agents might have been the deleterious factor. In general, it was found that when petit mal was controlled most effectively, grand mal tended to be precipitated most frequently.

Drug synergy: Prenderol appears to have a synergistic effect both with Tridione and Paradione. As previously stated, most patients with petit mal had been treated with other drugs without benefit. In 11 instances in which petit mal was incompletely or poorly controlled by Prenderol and the retarder alone, or by Paradione or Tridione alone, a combination of Prenderol with one of the "dione" drugs was effective. In eight cases synergy with Paradione was productive, and in three instances synergy with Tridione was equally productive. The experience with these 11 cases, which are included in this study in the group benefited by Prenderol, suggests that a combination of Prenderol and Paradione may be more desirable than one with Tridione.

Toxic effects: Prenderol proved surprisingly free from toxic side effects. Several patients reported occasional gastrointestinal upsets and a few episodes of dizziness when very high dosages were employed, but the manifestations were not severe enough to warrant discontinuation of medication. No rashes or pathologic urinary, blood, or liver profile findings were noted in any of the patients who took the drug. Sudden withdrawal of Prenderol did not create a

petit mal status. In general, statements regarding the toxicity of any drug like Prenderol that has been used for a relatively short time on relatively few patients must be made with caution. In this connection, it should be remembered that even in the case of Tridione and Phenurone, toxic effects were reported only after a large number of patients had been studied.

Effect on electroencephalogram: Unlike Tridione,[9] Prenderol effected control in many patients with petit mal without establishing normalization of the electroencephalogram. In four patients in whom control was completely established by Prenderol, normalization of the electroencephalogram was noted. In two patients the findings have remained normal for more than a year; in two patients re-abnormalization has occurred with recurrence of domes and spikes after periods of two months and four months, respectively. In neither patient has there been a recurrence of seizures.

COMMENT

Since petit mal seems more resistant to control by drugs than grand mal, any drug that offers a possibility for alleviating this condition is indeed welcome. Prenderol was found to serve this purpose. While not as effective as Tridione in petit mal, Prenderol nevertheless seems more efficacious than Paradione. Prenderol was definitely more beneficial than Phenurone, Mebaral, Milontin, Mesantoin, Gemonil, and other drugs for which some benefit has occasionally been noted in petit mal cases. Prenderol is most effective in petit mal of the idiopathic variety. Like Tridione, however, it may aggravate grand mal spells. Following the administration of Prenderol, remissions of petit mal seizures may occur just as readily as is the case of other established drugs. With Prenderol, however, the rate of recurrence is greater than that observed when Tridione is used, possibly because normalization of the electroencephalogram frequently takes place with the latter. In order of effectiveness in the treatment of petit mal, Tridione is apparently most effective, with Prenderol second, and Paradione third; but in terms of toxicity, Prenderol appears least toxic and Tridione most toxic. It might therefore be advisable to use Prenderol as the initial trial drug in the control of petit mal.

The effectiveness of the drug is most apparent when a retarder, in the form of cream, butter, or olive oil, or in the form of non-caloric retarders such as PVP or methyl cellulose, are added. Because of the advantages produced by adding a retarder, it is hoped that future forms of medication will include this important agent. In the control of petit mal, Prenderol seems to have a synergistic action with Paradione and Tridione, especially the former. The muscle-relaxing effect produced by Prenderol when administered to the cerebral palsied patient appears limited to patients with athetosis, and even here is not uniformly effective. The great advantage of the drug lies in its relatively non-toxic reaction and its tolerance by patients.

SUMMARY

1. Prenderol is effective in controlling petit mal, especially the idiopathic form.
2. The drug may aggravate grand mal spells.
3. Retarders are necessary to potentiate the action of Prenderol.
4. Synergistic action occurs with Paradione and Tridione, particularly the former.
5. Prenderol has occasional muscle relaxing effects on patients with tension athetosis.
6. Prenderol is relatively non-toxic.

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The attacks which most frequently consist only of clonic spasm are slight fits of partial distribution, beginning in, and often confined to, one limb. The most perfect type of these attacks are those which are sometimes produced by organic brain disease, and Hughlings Jackson has proposed to designate them "epileptiform convulsions" as distinguished from ordinary epileptic fits. But such local attacks of clonic spasm sometimes occur in cases in which there is no other reason to believe that there is such disease as tumor, etc., and in which the variable position of the local fit, and other symptoms, preclude the supposition that the symptoms are due to any fixed, coarse, organic disease. These local clonic convulsions are especially common in the upper limb, beginning in the hand. First the fingers begin to twitch, then the elbow is jerked, and the shoulder. The attack may then cease, or the face or leg may be jerked in the same manner. Consciousness is often not lost if the spasm is confined to a single limb. Less commonly these attacks begin in the face, and still less commonly in the leg.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Tumors of the Temporal Lobe

R. R. J. Strobos, M.D.

A SURVEY has been made of the patients treated for temporal lobe tumors at the Neurological Institute during the last ten years. In 62 patients, there was reasonable certainty that the tumor was limited to the temporal lobe and did not involve adjacent structures. In 18 patients this was proven by autopsy, and in each of the 44 others it was confirmed by combined air studies and surgical exploration. In 34 patients the right temporal lobe was involved, in 28 the left.

The findings in this series and in eight series reported in the literature[1-8] are presented in table 1.

PAPILLEDEMA

Papilledema was present in 34 patients. Among the 28 patients without papilledema, the cerebrospinal fluid pressure was within normal limits in 13 and slightly elevated in four.

AUDITORY SYMPTOMS

In the present series of patients, tinnitus occurred with equal frequency as an epileptic precursor or as an isolated phenomenon. It was most often perceived bilaterally, but, if unilaterally, it occurred with equal frequency on the ipsilateral and contralateral sides. The tinnitus, when not preceding epileptic attacks, had a sporadic and intermittent character.[1] Hearing was somewhat impaired in only four patients, in each instance to an equal degree on both sides. Two of these patients had audiograms which showed only a slight loss for higher tone perception.

A review of the literature also shows little difference in auditory acuity of the ipsilateral or contralateral ear. Gibbs[3] found hearing disturbances to be more frequently associated with tumors of the occipital lobe, the caudate or lenticular nuclei, or the thalamus than with temporal lobe tumors. It is well known that increased intracranial pressure in itself may cause congestion of the blood vessels of the inner ear and result in impairment of hearing.[9]

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TABLE 1

SYMPTOMS AND SIGNS IN TEMPORAL LOBE TUMORS IN PERCENTAGES*

	Neuro. Inst. of N.Y. 1941-1951	Cushing[1]	Kolodny[2]	Gibbs[3]	Keschner, Rowe[4]	Bender, Strauss[5]	Collins[6]	Sanford, Bair[7]	Biemond[8]	Average
Number of patients	62	59	38	197	52	110	57	211	112	—
Papilledema	55	—	87	—	81	—	63	65	—	67
Tinnitus	15	19	—	—	25	3	—	—	—	13
Complex auditory hallucinations	2	0	0	1	2	2	—	—	0	1
Impairment of hearing	6	12	8	6	17	—	4	—	—	8
True vertigo	18	—	—	—	—	—	—	—	—	18
Nystagmus	6	25	13	8	—	—	—	9	13	11
Olfactory and gustatory hallucinations	29	24	18	—	12	7	18	—	11	15
Impairment of smell	3	—	3	—	0	—	—	—	—	2
Contralateral homonymous field defects	34	56	32	—	58	—	54	58	22	46
Complex visual hallucinations	8	22	—	11	—	2	2	5	—	8
Signs of sensory aphasia (lesions on dominant side)	26	—	32	28	15	—	30	—	47	31
Epileptic seizures in general	55	—	50	—	37	—	47	—	51	49
Grand mal seizures	34	34	13	24	19	—	18	—	21	24
Dreamy states without generalized seizures	32	41	18	—	6	2	18	—	19	18
Mental changes	71	—	—	—	50	94	33	—	—	68
Headache in general	74	—	100	—	94	—	75	—	—	84
Headache ipsilateral to tumor	32	—	21	—	—	—	—	—	—	28
Ipsilateral facial pain	6	—	8	—	10	—	—	—	—	8
Pupillary inequality	13	—	45	—	23	—	9	18	21	19
Ipsilateral miosis	10	—	45	—	0	—	7	9	15	12
Ipsilateral ptosis	2	—	11	—	23	—	—	2	15	8
Ipsilateral partial or complete 3rd nerve paralysis	3	—	5	—	—	—	—	1	6	3
Ipsilateral diminished corneal reflex	3	—	18	—	—	—	—	—	11	10
Corticospinal tract signs, often minimal	84	—	87	—	50	—	—	—	82	76
Corticospinal tract signs contralateral to tumor	74	—	79	—	46	—	—	—	—	66
Ataxia of extremities	9	—	—	—	—	—	16	—	—	13
Truncal ataxia	11	—	3	7	—	—	—	—	—	7
Incontinence	3	—	21	10	—	25	—	—	—	14

* (—) means that no accurate figures are available.

Therefore, it is doubtful whether diminished auditory acuity has any localizing significance in tumors of the cerebrum. Only an occasional observer takes exception to this statement.[4]

Complex auditory hallucinations which are rare in temporal lobe tumors were present in only one patient of the present series. In a special study of this symptom Courville[10] found these hallucinations in only four of 99 patients with temporal lobe tumor and noted that they occurred more frequently with frontal lobe tumors. This was confirmed by Gibbs.[3] Courville states, however, that when such hallucinations occur in cases of frontal lobe tumor there are always additional signs of marked intracranial hypertension and severe mental changes, while this is not necessarily so in temporal lobe tumors. In the absence of these latter findings, therefore, complex auditory hallucinations may be of localizing value.

VESTIBULAR SYMPTOMS

Eleven patients complained of true vertigo. Cushing also stated that vertigo is not unusual in temporal lobe tumor.[1]

Four of the 62 patients had nystagmus, only present on lateral gaze, bilateral in one, and in the other three upon looking towards the side of the lesion.

OLFACTORY AND GUSTATORY SYMPTOMS

Olfactory or gustatory hallucinations were present in 18 patients. In the majority these hallucinations were purely olfactory in character, but occasionally an additional sensation of taste was reported. Pure gustatory hallucinations were rare. In nine patients they only occurred as an aura in epileptic attacks; in the other nine they occurred independently, but might occasionally be followed by epileptic attacks in a later stage of the illness.

One other patient noted perseveration of taste. After an epileptic attack before which she had been eating chocolate, everything tasted like chocolate for a week. Another patient had to abstain from certain beverages because the smell became unbearable.

The sensation of smell was impaired in only two patients, bilaterally in one, contralaterally in the other. The sensation of taste, where examined, was never disturbed.

VISUAL SYMPTOMS

In 31 patients the visual fields were examined by perimetry or the tangent screen. Fifteen of these were shown to have contralateral homonymous field defects, of which six were limited to the upper quadrants and one to the lower quadrants, while eight showed a hemianopic defect. A strict symmetry of the visual field defects was demonstrable only in those cases presenting a complete hemianopia without central sparing. In the 15 patients with field

defects central sparing was present in five, was not present in five others, while in the remaining five patients only peripheral parts of the fields were involved. Of the 31 patients in whom perimetry was not performed because of unreliability due to youth or poor condition, six seemed to have homonymous hemianopia on gross testing.

In general, there is agreement that visual field defects in temporal lobe lesions usually lack the strict symmetry that is encountered in occipital lesions. Central sparing occurs in occipital lobe lesions, but may be absent in instances of involvement of the optic radiation in the temporal lobe.[7,11,12] This was demonstrated in two of our patients who, after temporal lobectomy, showed field defects in which central vision was not preserved, while before operation the fields had been intact.

Five patients in the present series complained of complex visual hallucinations, which were always associated with a diminished awareness for the environment without complete loss of communication. One of these patients occasionally had associated olfactory hallucinations, and in two others visual hallucinations were sometimes followed by grand mal seizures. In none of these patients were the hallucinations localized to one side of the field. In two of the five patients with these complex visual hallucinations a vestibular component seemed inherent to the episodes, in that there was rapid movement of the hallucinations in one direction as well as a sense of movement.

Complex visual illusions were present in two patients: one constantly saw the hands of people crippled and deformed only in the contralateral field of vision, while the other suffered from episodes in which all objects started to shake and multiply, so that finally several identical images were present at the same time. This symptom has been described as multiopia[13] or visual spread.[14] In connection with the explanations brought forward, it may be of interest to note that this patient had no impairment of visual acuity and had normal visual fields.

Elementary visual hallucinations were present in four patients and in two instances were of a hemianopic character with hemianopia present on examination.

APHASIA

Of the 16 patients with signs of aphasia, 14 were right-handed with a left-sided tumor, while in two definitely left-handed patients the tumor was on the right side. Three of the aphasic patients suffered only from anomia. In the other 13 symptoms of sensory aphasia were more fully developed, and in ten there was a clear history that the symptoms had progressed from an initial anomia with paraphasia in a later stage and only finally difficulties in understanding speech. This sequence of events has also been described in the literature.[2,9]

EPILEPTIC SEIZURES

Thirty-four patients of this series had epileptic attacks, and different types of attacks frequently occurred in the same patient.

Twenty-one patients had attacks of loss of consciousness with generalized tonic-clonic convulsions. In 11 patients these occurred without warning; in the other ten an aura preceded the attack. In nine of these patients a warning period occurred, characterized by some degree of confusion and often inability to speak, which was associated with complex visual hallucinations in two patients, with olfactory hallucinations in one, and with tinnitus in one. The tenth patient heard only buzzing noises and did not recall any confusion before the grand mal seizure.

There were six patients who had attacks of loss of consciousness without convulsive movements, and two of these had preceding olfactory hallucinations.

Twenty patients had episodes of confusion without subsequent generalized seizures or loss of consciousness. These episodes were always associated with other phenomena, such as incoherence of speech, facial pallor, vacant expression, twitchings of the mouth or jaw, or similar signs. In seven patients these episodes were preceded by olfactory hallucinations, in two by hallucinations of taste, in one by peculiar abdominal sensations, and in one by tinnitus. Confusion was present to a varying degree in different patients. Three patients had no recollection of these episodes afterwards and the confusion was noted only by observers. Three patients described the attacks as a typical feeling of derealization, one as depersonalization, one as déjà vu sensation. Five patients experienced episodes of complex visual hallucinations, four had dreamy states without further specification, one a vague recollection of former experiences, one a feeling of impending disaster, and one had what she could only describe as "a feeling of suspended animation."

There were 23 patients who had either minor seizures with some degree of impairment of consciousness without complete loss of consciousness, or similar episodes prior to generalized seizures. Since epileptic seizures in one form or another were present in 34 patients, the majority of epileptic patients suffered from such episodes. There is reason to believe that these attacks are more common in anteriorly-situated tumors, because 17 of these 23 patients showed no field defects. The episodes differ from petit mal, in that they occur far less frequently and have a longer duration. There was only one patient in this series with true petit mal seizures.

In 20 of the 34 patients with seizures these were the first symptom to occur. In five others they appeared before there were symptoms of increased intracranial pressure, and in only nine did they occur thereafter. Among the latter were two patients with attacks of clonic contractions of extremities contralateral to the tumor without loss of consciousness, a rare occurrence in temporal lobe tumors.[3]

In this series there were three children under age 15. Two of these had epileptic attacks and in addition showed peculiar behavior disorders worthy of comment. One girl of 12 years had had for three years attacks of almost psychotic behavior in which she cried and screamed, and was abusive, disobedient, and aggressive towards herself and others. She suffered from a left temporal lobe astrocytoma. The attacks disappeared for at least half a year after surgical intervention. Another girl of 12 years had shown for the last two years sudden episodes of extreme irritability and stubbornness that bore no relation to outward circumstances and were so incongruous with her usual self that the parents spontaneously used the expression "a dual personality." In this patient there was a left temporal spongioblastoma polare. In none of the other patients was anything similar observed. It might well be that episodes of impaired consciousness in adults who have a more highly developed integration of the personality only lead to some confusion and a change in the relation to the self and the environment, while in the less integrated personality of the child with its easier convertibility of thought and impulse into action the same impairment may give rise to this particular psychopathic behavior.

MENTAL SYMPTOMS *(apart from those with epilepsy)*

Of the 44 patients with mental changes, two showed only loss of memory for recent events. The most frequent change consisted of a gradual slowing of cerebration, loss of memory, and apathy. This occurred in 34 patients, and 13 finally came to a chronic state of confusion, drowsiness, and, in some instances, stupor. These changes are probably related to intracranial hypertension and have hardly any localizing significance.[4,5] In all of these patients there were definite signs of increased pressure, as evidenced by papilledema or upon measurement during lumbar or ventricular puncture. Moreover, in 22 patients the mental symptoms appeared late in the course of the disease, after symptoms of increased pressure like generalized headaches and vomiting had been present for some time.

There was one patient with euphoria and no other mental changes; this patient also had papilledema. There were seven patients with more complicated mental changes, in four of whom there was evidence of intracranial hypertension. In these patients the mental symptoms seemed to represent a reaction to the disease or to the epileptic attacks, and were related to the premorbid personality. These changes consisted mostly of psychopathic personality changes, paranoid trends, hypochondriac ideas, fear of insanity, or extreme irritability. Several of these patients had extensive psychiatric examinations which confirmed this impression.

It is not justifiable from these data to attach too much localizing value to these mental changes. In most instances of temporal lobe tumor, the frequency of mental changes is probably due to the early appearance of

TABLE 2

THE MOST FREQUENT SYMPTOMS AND SIGNS IN TEMPORAL LOBE TUMORS, AS REPORTED IN NINE SERIES[1-8]

Symptoms	Per Cent	Signs	Per Cent
Headache	84	Corticospinal tract signs	78
Mental changes	68	Papilledema	67
Epilepsy in general	49	Contralateral homonymous	
Grand mal seizures	24	defects of the visual fields	46
Dreamy states	18	Sensory aphasia	31
Vertigo	18	Pupillary inequality	19
Olfactory and gustatory			
hallucinations	15		
Tinnitus	13		

(These figures are taken from the last column of table 1.)

increased pressure. Mental changes are reported frequently in the literature, and are generally consistent with the above description.

OTHER SYMPTOMS AND SIGNS

A few other symptoms and signs may be mentioned briefly, mainly in connection with their frequent occurrence or lateralizing value.

In our series headache had a definite lateralizing value: 20 of the 46 patients who complained of headache experienced this far more noticeably or even exclusively on the side of the tumor, while it was more pronounced on the opposite side in only one patient. In some of the series of the literature[2,15] this feature is also apparent.

Corticospinal tract signs are extremely frequent though often minimal. In most instances they lateralize the lesion correctly. They were ipsilateral to the tumor in only six of the patients. There was no predilection for greater involvement of the facial muscles. This sometimes occurred, but in an equal number of patients the extremities showed more definite signs than the face.

Pupillary inequality was seen in eight patients, in six of whom the ipsilateral pupil was smaller than the opposite one. In most series in the literature[2,4,7,8] this sign is more frequently present, and miosis on the ipsilateral side is seen most often and sometimes even exclusively.[2,6,8,15] In only one series was ipsilateral mydriasis exclusively present.[4] Kolodny[2] discusses this sign extensively and argues that the initial miosis is due to pressure on the sympathetic fibers accompanying the first branch of the trigeminal nerve. Ptosis usually follows later, caused by the same mechanism. Only in a much more advanced stage of the disorder do we find oculomotor compression with paralysis and ipsilateral mydriasis. This line of reasoning is accepted by most observers.

The occurrence of ataxia is accepted by most authors as due to involvement of either the vestibular projection area in the temporal lobe or the temporo-ponto-cerebellar pathways.[4,16,17]

Incontinence was seen only in very late stages of the disease.[2,5]

For other signs and symptoms refer to table 1.

SUMMARY AND CONCLUSIONS

In the last column of table 1 the frequency of the different symptoms and signs is expressed in percentages. These percentages are taken from the sum of all the series so far as specific figures were available for the symptom or sign under consideration. In table 2 the percentages of the most common symptoms and signs are arranged in order of frequency. From the available data it appears that seizures are a frequent symptom in temporal lobe tumors and usually occur early in the course of the disease. These often take the form of episodes of defective consciousness without complete loss of consciousness, and may then be experienced subjectively as episodes of depersonalization and allied conditions, dreamy states with or without complex visual hallucinations, or confusion, or more rarely may appear as episodes of automatic behavior with retrograde amnesia. Epilepsy may also be present as attacks of loss of consciousness with generalized convulsions or, occasionally, without these.

Olfactory and gustatory hallucinations, vertigo, or tinnitus occur as an aura in epileptic seizures or independently.

Headache is a very common complaint. Mental changes, most frequently those associated with intracranial hypertension, are present in the majority of patients and are in dominant hemispheral tumors, often accompanied by signs of sensory aphasia, which presents itself at onset as pure anomia.

Aphasia and contralateral homonymous visual field defects are the most important localizing signs with respect to seat and side of the tumor. Other signs may help in lateralizing the lesion, especially corticospinal tract signs. The side on which headache is experienced most severely, and in an early stage of the disease the side on which the pupil is smallest, may be of additional help in lateralizing the disease process.

The above description adds up to a rather clear-cut clinical picture when it occurs. However, to prevent overconfidence in this regard, it must be emphasized that we have studied the patients in connection with the presence of some of the more typical symptoms and signs: 1) epileptic episodes with impairment of consciousness, without loss of consciousness as defined above; 2) olfactory and gustatory hallucinations; 3) tinnitus; 4) true vertigo; 5) sensory aphasia; and 6) contralateral homonymous field defects. We use the expression "more typical" deliberately and are well aware that there is no sign or symptom that is exclusively present in temporal lobe disease, the diagnosis of which still has to be made through consideration of all the available evidence.

Forty-one of the 62 patients showed only one or two of these six considered symptoms and signs in approximately equal proportion, 11 patients

showed three or more of them, but there were ten patients in whom none of them appeared. This, however, is probably an exaggerated number, due to the criteria by which this series was chosen. In the last ten years there has not been a uniformly consistent policy as regards the desirability of air studies before operation. Consequently patients were sometimes operated upon without air studies, when there was no doubt about localization of the tumor. These have not been included in this series. On the other hand, all patients without any localizing symptom or sign, in whom there was suspicion or certainty of the presence of the tumor, had air studies. This series was chosen from a large group of patients, and it was deemed necessary to have air studies as additional evidence to choose the tumors restricted to the temporal lobe besides operative removal. In this way these must appear an unavoidable tendency in favor of the patients without localizing signs or symptoms.

In the ten patients without signs and symptoms more typically referable to the temporal lobe, the tumor was on the right side in six instances (of 34 right-sided tumors) and on the left side in four (of 28 tumors), an almost equal proportion. This indicates that the non-dominant temporal lobe is no more silent in its symptomatology than the dominant lobe.

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Actinomycosis of the Nervous System

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THE last comprehensive survey of the problem of actinomycosis of the central nervous system was published in 1936 by Friedman and Levy.[1] Since that time two important developments have occurred: 1) the advent of chemotherapy, and 2) more extensive knowledge of the clinical, cultural, biologic, and morphologic characteristics of the several organisms that cause actinomycosis. Almost universal acceptance has been accorded the new classification of Waksman and Henrici (1943) which now separates actinomycosis into 1) true actinomycosis due to Actinomyces bovis, and 2) nocardiosis, due to Nocardia asteroides.[2] Earlier reports made no distinction or rejected this classification. Not only is the differentiation important for scientific exactitude, but it is also justified on practical clinical grounds.

Actinomyces bovis is Gram-positive, anaerobic, and non-acid-fast, and usually produces sulfur granules in the tissues which are associated with radially-disposed filaments whose ends are swollen to form eosinophilic "clubs." This constellation is responsible for the name "actinomycete" (ray fungus). The primary lesions of Actinomyces bovis are found chiefly in the cervicofacial connective tissue, less often in the thoracic and abdominal viscera.[3] Nocardia asteroides, described by Nocard in 1888, is a Gram-positive, aerobic organism, which is more or less acid-fast.

Both organisms may invade the central nervous system and produce morbid changes which are indistinguishable for practical purposes.[4–6] Both are rare causes of central nervous system disease, particularly Nocardia. At present, mycologic studies in clinical cases are usually so incomplete that precise data are not available on the relative frequency of the two types of actinomycosis, but it is generally conceded that nocardiosis is the rarer. The preponderance of Nocardia infections that are reported as such involve either the lung or the central nervous system, and in the latter there is usually evidence that the disease metastasized from the lung to the brain. In 1946 Kirby and McNaught[6] reported two new cases of nocardiosis and found 32 prior

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descriptions in the literature. Pulmonary involvement appeared in 29, 11 of which had metastases to the brain. In 1949 Tucker and Hirsch[7] added three more new cases and found 37 cases in the literature with the lungs affected in 33, 11 of which developed metastases to the brain. Moersch[8] reviewed the world's literature on actinomycosis in 1922 and found 48 cases affecting the nervous system; in addition, he reported 18 cases involving the central nervous system out of a total of 74 cases. No etiologic distinction was made between the two types of actinomycosis. Similarly, in Friedman and Levy's review,[1] no classification of their 108 cases was made.

Clinically, the neurologist is justified in regarding the generic entity, "actinomycosis," valid and practical. The diagnostic criteria are similar for both causative agents, and both are secondary to a chronic purulent infection elsewhere which spreads either by direct extension or by metastasis. Primary cerebral involvement has been claimed in a few instances but discounted by most.[1,4,5]

Generally, the manifestations of actinomycosis are superimposed on a chronic suppurative infection involving the cervicofacial area, the thorax, or abdomen. Rarely a subcutaneous purulogranulomatous lesion of the toes may constitute the original infection, that is, madura foot. This latter is considered to be due to Nocardia in most instances,[2] and it also may be the primary source for metastatic brain lesions.

Invasion of the central nervous system by actinomycosis is usually declared by the appearance of signs of 1) abscess, 2) meningitis, or 3) both. In spite of attempts by some to ascribe specific qualities to actinomycotic abscess or meningitis, the consensus holds that there is no reliable distinguishable clinical difference from bacterial disease affecting the same structures.

The cases reported here illustrate some of the clinical features that suggest the diagnosis. However, confirmation comes from the laboratory. Material obtained from the draining sinuses, abscess, spinal fluid, and so on should be subjected to immediate microscopic examination and cultured on the media conventionally employed to develop growth of mycotic organisms.[9] Anaerobic and aerobic culture is necessary, and particular care must be used in the staining and decolorizing procedure to demonstrate the acid-fast quality of the suspected organism. Animal inoculation may be of further aid. Spinal fluid examination and culture are often disappointing, particularly in actinomycotic brain abscesses. As in other forms of brain abscess, the spinal fluid may show minimal or no changes; for example, Lewin and Morgan[10] found eight out of ten spinal fluid examinations to show normal constituents in their case.

In addition to abscess and meningitis, a rare and curious manifestation of cerebral actinomycosis is actinomycoma. Orr[11] enumerated four cases involving the floor of the third ventricle, one involving the orbit, and his own case which was diagnosed as ball-valve colloid cyst of the third ventricle. At autopsy, this latter was found to be an actinomycoma associated with marked internal hydrocephalus.

A similar actinomycoma was observed below the cortex in the first case described below. Aside from this unusual granulomatous tumor, the rest is quite representative of cerebral actinomycosis (nocardiosis).

Case 1.—A 35 year old white man was admitted to Mt. Alto Veterans Hospital for the first time on July 7, 1951, with a chief complaint of frontal headache and blurring of vision in the left eye. About one year before the patient observed an abscess on his right buttock which was incised and drained several times by his physician; penicillin was administered by injection. About one month prior to hospital admission the patient suffered a sudden attack of unconsciousness which lasted about half an hour. He was admitted to another hospital at that time where examination revealed left hemiparesis, a left Babinski sign, stiff neck, and bilateral choked disks; an abscess on the right chest which had appeared several weeks before was aspirated and purulent material was obtained; smear and culture revealed no organism.

On the day of admission the patient was physically normal aside from carious teeth, the scar of the previous incision and drainage of the abscess, and a non-fluctuant mass beneath the right nipple. The neurologic examination showed no nuchal rigidity. Station, gait, and coordination were intact, and muscle strength and tonus were equal and normal. There were 4 diopters of choking bilaterally with small peripheral hemorrhages. The pupils were slightly dilated, equal, reacted to light and in accommodation; extraocular movements were normal. Sensation was unimpaired. The deep tendon reflexes were brisk, and there was a bilateral Babinski sign. The psychiatric examination showed a slightly obtunded man with impairment of memory, particularly for recent events. However, he was correctly oriented. The impression at that time was brain abscess, probably due to a granulomatous lesion, metastatic in nature. An electroencephalogram done the same day showed a diffusely disorganized pattern with frequent 4 to 6 per second irregular waves appearing in all leads, predominately in both frontal leads and in the temporal, anterotemporal, and frontal leads on the left. Phase reversal phenomena emanated from these latter sites. Hyperventilation produced marked buildup with sustained generalized dysrhythmia (figure 1). A ventriculogram done on July 9, 1951, showed marked downward displacement of the left anterior horn with displacement to the right. The radiologist's impression was "space-occupying lesion in the left frontoparietal junction." The spinal fluid examination done on the same date showed a total protein of 36 mg., a cell count of 9 white cells, and no evidence of any organism. None was cultured from the spinal fluid and three subsequent spinal fluid examinations showed only slightly elevated total protein.

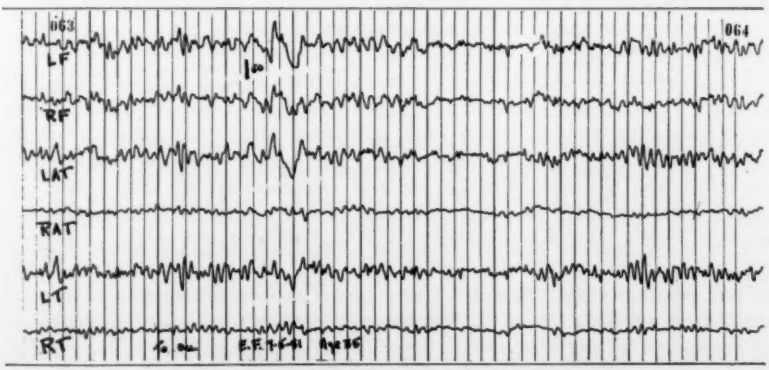

FIG. 1. *Case 1.* Electroencephalogram showing left frontotemporal focus.

The patient was placed on antibiotic therapy, and a craniotomy was performed with removal of a well-encapsulated thick-walled granuloma (figure 2) from the posterior third of the left frontal lobe. Following this the patient continued to improve for the next several weeks, when signs of increased intracranial pressure began to reappear. During this time multiple aspirations for smear and culture from the right anterior chest wall lesion were made, but no organism was found. The granuloma removed at operation was also examined for fungi and other organisms. On September 7, 1951, another ventriculogram was performed which showed a shift of the ventricular system to the left (figure 3). Re-operation showed an extensive abscess through the entire frontal fossa on the right side. Again the patient responded well to surgery, the papilledema receded, and two days postoperatively he was alert and moving all extremities. Improvement continued, but x-rays of his chest continued to show an opacity in the right lower lung.

One month after the second operation the patient was in excellent condition and was discharged, only to return five days later because of a generalized convulsion while at home. The spinal fluid contained 34 mg. of protein per 100 cc. and 8 cells per cu. mm. Neurologic examination at that time showed minimal blurring of the disks and clonus of the left ankle and patella. The temperature remained elevated and spinal fluid examination revealed increased pressure. On November 23, 1951, material cultured from the anterior chest wall abscess revealed Nocardia asteroides. By this time the patient's spinal fluid pressure was 480 mm., there was choking of the disks, and the brain was bulging through the skull defect on the left side. The patient was lethargic and attempts to relieve the intracranial pressure by aspiration of the left frontotemporal areas were ineffectual. He lapsed into coma and died on November 28, 1951.

At autopsy the exterior surface of the brain was normal aside from the evidence of previous surgical manipulation. Coronal sections of the frontal lobes showed a more or less circumscribed mass in the left lobe. It had a greenish-yellow color and was soft in consistency. The diameter was 1.5 cm. and it extended for a distance of approximately 3 cm. A similar lesion was found in the posterior-superior aspect of the genu of the corpus callosum. Other lesions were found throughout the parietal and occipital lobes and cerebellum. One of these abscesses from the frontal lobe, when studied microscopically, showed a well-circumscribed abscess with a cavity filled with polymorphonuclear leukocytic exudate which was largely necrotic and in which the cells stained very poorly. The wall of the abscess was composed of granulation tissue, and the surrounding brain tissue was moderately edematous, showing large amounts of phagocytized blood pigment with congested neighboring vessels (figure 4). Nocardia asteroides was identified in this and similar lesions throughout the brain (figure 5).

The rest of the autopsy was essentially negative aside from pulmonary congestion, edema, and a terminal, patchy, confluent bronchopneumonia of both lower lobes.

This patient's course showed the characteristic sudden and wide changes in clinical status that typify many of the cases of cerebral actinomycosis described by other authors. These rapid alterations often occur independent of any particular therapy. The long course of the disease, difficulty isolating the organism, and the fatal outcome are also representative of central nervous system actinomycosis. Nocardia asteroides is much more likely to invade the nervous system than Actinomyces bovis,[13] and the isolation of this organism justified a gloomy prognosis. This demonstrates another reason for a more refined laboratory diagnosis of the mycoses. The long duration of actinomycosis often belies the gravity of the infection, and an explosive manifestation of neurologic involvement usually signalizes the beginning of the inexorable decline of the patient. The following case again illustrates this principle and

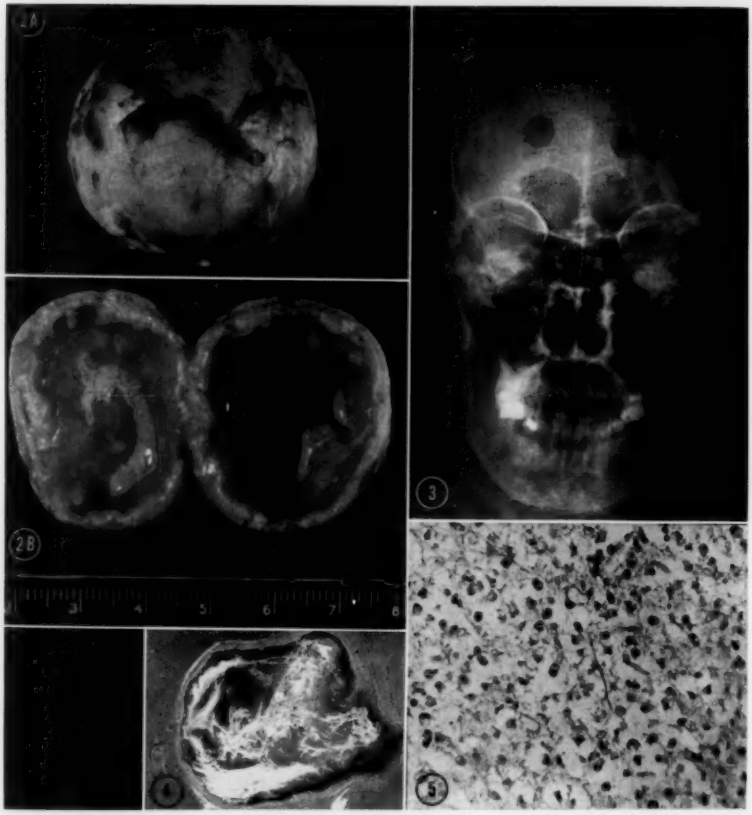

FIG. 2A and 2B. Mycetoma, showing viscid gelatinous fluid on inner wall. FIG. 3. Ventriculogram September 7, 1951, showing marked displacement of ventricles to the left. FIG. 4. Typical abscess. Hematoxylin and eosin stain. FIG. 5. Hyphae of N. asteroides in brain abscess. Acid-fast stain. Figures 2 to 5 illustrate case 1.

provides a striking example of chronicity, since the disease remained static at least 18 years and extended over a total period of 25 years.

Case 2.—The patient was a colored woman who worked in the hayfields and tobacco fields until the age of 17. At age 35 she noted a "hole in her side" which drained pus intermittently, but for which she sought no treatment. On April 27, 1945, at age 53, the patient was found unconscious in bed and was admitted to Gallinger Municipal Hospital in coma. The deep tendon reflexes were universally depressed; there was slight nuchal rigidity, but no focal signs. Blood pressure was 110/60, pulse 96, respirations 36, temperature 99° F. In addition to scars of old healed sinuses over the flexor surfaces of the proximal phalanges of the toes of the left foot, there was found in the seventh right interspace, in the axillary line, a draining sinus tract from which copious purulent fluid exuded

with coughing. Small fragments of necrotic bone and soft tissue were removed from this site and crushed between slides; under the microscope numerous mycelia were seen. Culture of this material revealed "actinomycosis." Multiple cultures and smears were made and at various times numerous other organisms were obtained. She was discharged on June 5, 1946, without fever or other symptoms. She regained her weight and strength, and was readmitted on August 11, 1950 for surgical repair of her draining sinus, at which time the culture was again positive for actinomycosis. On August 25, 1950, the penicillin and sulfonamide treatment was stopped for five days, at which time the patient had a left-sided Jacksonian seizure and lapsed into profound coma. There were no focal signs and no nuchal rigidity. Her condition improved rapidly and she refused any surgery. She was discharged ambulant and afebrile on October 10, 1950, to be readmitted on January 3, 1952, because of nausea and vomiting. Her temperature was 99.4° F., blood pressure 140/80, pulse 112. Four days later she suddenly became confused, disoriented, and irrational. The lethargy increased and eight days after admission, while being draped for a lumbar puncture, she developed generalized rigidity, opisthotonos, and cyanosis. A left hemiplegia appeared with deviation of the tongue to the left and a positive left Babinski sign. However, she improved rapidly over the next two days, and two weeks after admission she was again alert and asymptomatic. She was discharged, to be readmitted on April 28, 1952, because of dyspnea. At that time she was lethargic and speech was slurred. She became increasingly comatose and died on May 3, 1952. No autopsy was obtained.

Again, the characteristics of the actinomycoses are shown—the chronicity, sudden appearance of neurologic involvement, remissions and exacerbation, and so on. The patient survived seven years after the appearance of neurologic involvement. Because of the old healed sinuses in the foot, this case might be classified as maduramycosis, which usually is due to a Nocardia and characteristically has a hematogenous spread, in contrast to Actinomyces bovis which is more likely to invade by direct extension. In addition to the presence of the rare syndrome of maduramycosis, another rather uncommon feature of this case was the occurrence of actinomycosis in a woman. Men are much more vulnerable. One further important facet of this problem is demonstrated by the presence of bacteria in the draining sinus in the chest wall of this patient. This poses the question of whether these bacterial agents might not be the chief or supplementary etiologic factors in the metastatic brain abscess rather than the fungus. However, secondary brain abscess is more likely to be bacterial, or mixed, in Actinomyces bovis than in nocardiosis,[14,15] illustrating another difference between the two fungi and one which might influence therapeutic management. In this same connection, the prolonged use of chemotherapeutic or antibiotic drugs in the treatment of actinocycoses might alter the ecology of the original site of the infection and breed a resistant bacterial organism which might then metastasize to the brain.[16,17]

The third case illustrates primary abdominal infection with Actinomyces bovis that possibly began in the appendix. Over a period of several years there were multiple and often inexplicable changes in the patient's clinical status, and even after implication of the central nervous system, seven months elapsed before death.

Case 3.—A 35 year old colored man was admitted to Gallinger Municipal Hospital in 1948 because of chronic abdominal pain. An appendectomy, cholecystectomy, and two

more laparotomies were done in that year. The latter two procedures were necessary to drain abdominal abscesses, and one such abscess continued to drain for the next four years. Otherwise the patient was asymptomatic until April 23, 1952, when he had an onset of chills, fever, frontal headache, and a feeling of fullness in the lower abdomen. At the same time he noticed a furuncle on his right forehead and another above the right twelfth rib anteriorly; a few days later he noted a mass in his right axilla. One week after onset, he consulted his private physician who gave him a penicillin injection and some sulfadiazine. There was no mitigation of his symptoms and he was finally admitted to the hospital on May 5, 1952.

At this time the temperature was 101° F., furuncles were noted on the forehead, and there was a tender swollen mass over the right chest wall. There were several tender nodules in the subcutaneous tissue of the right upper quadrant, and basal rales were noted bilaterally. Chest films showed a density in the right mid-lung field and infiltration at the right base with pleural effusion at the left base. Routine blood and urine examinations were negative, and cultures and smears from pus in the skin lesions, sputum, gastric washings, feces, spinal fluid, and blood were negative. However, on the tenth day sulfur granules were found in the pus, both from the abdominal abscess and from the axillary furuncle. A diagnosis of actinomycosis was made, and the patient was placed on penicillin, 600,000 units every six hours, and Gantrisin, 1 gm. every six hours. The spinal fluid examination on May 5, 1952, showed clear fluid, 5 cells, and a pressure of 180 mm.

In the fifth week after admission, a mild right hemiplegia developed associated with deviation of the tongue to the right and a positive Babinski sign on the right, but no changes in the fundi. Spinal puncture revealed no abnormalities of fluid or pressure, and skull films were negative. Streptomycin, 1 gm. twice a day, was begun at this time, and the central nervous system signs gradually cleared. The patient's general condition improved despite the persistence of lung cavities and the pleural effusion. He was discharged after 12 weeks of hospitalization, to remain on penicillin and Gantrisin.

He was readmitted on August 13, 1952, because of "black-out" spells and constant headache. The neurologic examination at that time was negative aside from weakness of the right leg. Spinal fluid examination revealed 110 mm. of pressure, a cell count of 12 (all lymphocytes), and normal chemical constituents. The patient was discharged against medical advice before the work-up was complete, only to be readmitted a few days later. His headaches had increased in severity, and his seizures had become more frequent. These latter were focal and began in the right side before they became generalized. He complained of poor vision, and there was marked weakness of the right foot. The neurologic examination on September 1, 1952, showed sluggish pupils, tremor of the protruded tongue, deviation of the tongue to the right, and slurred speech. A mild right hemiplegia was present. Spinal fluid examination at this time showed a pressure of 300 mm., 12 cells, 58 mg. of sugar, 126 milliequivalents of chlorides, 105 mg. per cent of protein, and a first zone gold curve. A ventriculogram performed on September 3, 1952, showed a slight shift of the ventricles to the left and displacement downward of the left frontal horn. An electroencephalogram was abnormal, showing high voltage slow waves throughout. The patient was given Gantrisin, streptomycin, and potassium iodide. After two days he became afebrile and was discharged on September 30, 1952.

Because of constant seizures he was readmitted on October 8, 1952, complaining of severe headache but having no fever. The neurologic examination showed right hemiparesis with increased deep tendon reflexes on the right. The right cremasteric and abdominal reflexes were absent, and there were positive Babinski and Hoffman signs on the right. The optic disks were flat and the pupillary responses sluggish. Two days after admission he became cyanotic, lapsed into coma, and died two days later.

The postmortem examination was negative aside from the cerebral findings. The brain was congested and the sulci flattened. A soft fluctuant area about 5 cm. in diameter was

found at the surface in the right occipital parietal area. After formalin fixation coronal sections showed multiple abscesses averaging about 2 cm. in diameter, sharply demarcated from the surrounding area (figures 6, 7, 8, and 9). Multiple stains were used, revealing a typical abscess, the central cavity tightly packed with polymorphonuclear cells, the surrounding parenchyma showing marked reaction with edema, dilation and congestion of blood vessels, decrease in nerve cells, and proliferating astrocytes and microglial elements. No Actinomyces were found, but the marked thickness of the abscess wall was suggestive of true actinomycosis, rather than nocardiosis.

The appendectomy in case 3 may have been necessary because of mycotic invasion of the appendix. This is presumably one source of abdominal mycosis, the fungus reaching the gastrointestinal tract possibly from the purulent pockets about carious teeth,[18] tonsils,[19,20] or similar oropharyngeal sites.[21] Of 21 cases of fatal actinomycosis reviewed by Weed and Baggenstoss,[14] 12 were of the abdominal type, eight of which were preceded or followed by appendectomy.

When central nervous system signs or symptoms appear, the presence of an established actinomycotic infection offers strong inferential evidence that an abscess or meningitic process due to the same organism has involved intracranial structures. Occasionally the neurologic disorder, for example convulsions, headaches, and so on, brings the patient to the doctor first,[22] as in case 2. In this latter event, correct diagnosis is suggested if the neurologist observes or obtains a history of chronic purulent drainage or pulmonary infection. Smear and culture of available exudate or spinal fluid should be requested, particularly to exclude tuberculosis. Anaerobic and aerobic cultures should be requested, as well as acid-fast staining with 1 per cent sulfuric acid rather than the stronger acid preparations usually used for decolorization. The relative simplicity of the technic for a laboratory diagnosis of actinomycotic infections has been emphasized by Binford and Lane.[23]

It should be emphasized that the laboratory culture of Nocardia on plates is dangerous.[24] Since there is a risk of inhalation of the arthrospores, the use of slants is recommended. The literature makes no mention of this risk. Identification of Nocardia is further confirmed by smelling its strongly rancid odor, both in the exudate[25] and in pure culture.[7] Sampling the odor through cotton plugs in slant tubes is considered safe, but open plates are hazardous. Actinomycoses are not contagious and no man-to-man spread of the disease has ever been reported. Even when the patient is excreting the organism in large numbers in sputum, pus, or feces, contact with this material does not transmit the disease.[26] A human bite, however, can produce actinomycosis.[3,27]

The lethal nature of cerebral actinomycoses is exemplified in three of the four instances recorded here. Earlier reports express pessimism over the outcome of actinomycoses, but hope was inspired with the advent of chemotherapy and antibiotics. This was further justified by the demonstration of in vitro sensitivity of the Actinomyces to sulfonamides and antibiotics.[28–30] However, Glover and others[31] reviewed the outcome of 36 cases of nocardiosis of various organs reported in the literature up to 1947 and found only four which could be considered cured. In all these four cases sulfonamides were

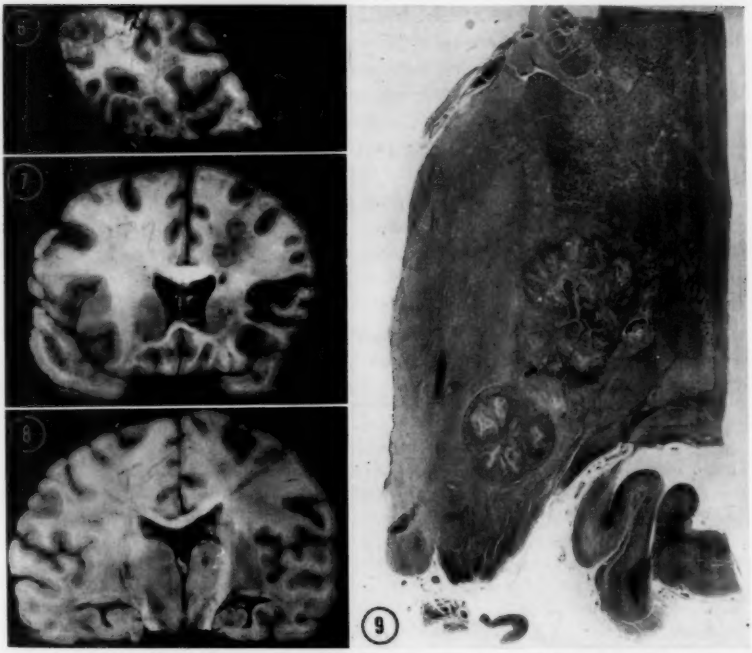

FIG. 6. Superficial nest of abscesses in occipital lobe. FIG. 7. Abscesses deep within white matter. FIG. 8. Abscess in internal capsule. FIG. 9. Masson stain, showing extremely thick abscess wall of dense collagen fibers, typical of A. bovis. Figures 6 to 9 illustrate case 3.

used, and the authors concluded that this is the preferred drug in nocardiosis. Weed and Bagenstoss[14] concur in this and deduce from their observations that penicillin is the drug of choice in the treatment of actinomycoses due to Actinomyces bovis. Other recent observers have used various combinations of therapeutic measures, including the older therapeutic agents, potassium iodide and x-ray, in treating the actinomycoses affecting various organs.[6,32,33] Penicillin has been given preference by some;[34–36] sulfonamides alone[37] and penicillin with sulfonamides by others.[38] Aureomycin,[39–41] Terramycin,[42–44] and streptomycin[45] have scored success in treating non-cerebral actinomycoses. Stilbamidine is one of the newer drugs found to be successful in one case reported by Miller and others.[46] Even more recently Lamb and his co-workers[47] credit Pregnenolone acetate in curing a mycetoma due to an atypical strain of Nocardia asteroides in a six year old girl. Surgical excision is an important adjunct to therapy in some cases of mycotic disease, according to a recent review by Baker.[48] This is demonstrated in case 4.

In contrast to actinomycoses elsewhere in the body, cerebral actinomycoses still imply a very unfavorable prognosis in spite of chemotherapy, antibiotics,

and surgery. Many recent reports testify to this.[6,7,10,13,14,22,23,49,50,51] The first claim of cure of central nervous system actinomycosis was made by Jacobson and Cloward[52] who treated a patient with meningitis and brain abscess due to Nocardia with sulfonamides, penicillin, and streptomycin, and also employed ventricular drainage for 12 days. However, their follow-up period has been less than seven months. Another seven month cure has been reported by Schneider and Rand[53] who drained a right frontoparietal abscess and treated the patient with sulfanilamide and penicillin. The smear and culture showed an organism "typical of actinomycosis," but no further designation is given. Tinsley[54] described the use of penicillin and streptomycin with drainage of a parietal lobe abscess due to Actinomycoses with recovery maintained after one year. A similar cure was effected in the following case:

Case 4.—A 44 year old white housewife was admitted to St. John's Hospital on May 15, 1945, with a two month history of headache, vomiting, unsteady gait, disorientation, and drowsiness. Physical examination showed a temperature of 98.6° F., pulse 74, respirations 20, and blood pressure 115/65. In addition to the hebetude, she showed ataxia of the left hand and decreased sense of position in the toes bilaterally. The spinal fluid was normal except for a one plus Kahn. The blood Wassermann was negative. In two weeks she developed choked disks and a sixth nerve weakness on the right. A diagnosis was made of "general paresis, possible brain tumor." Vital signs remained unchanged, but confusion and disorientation persisted and a moderate right hemiparesis, aphasia, and left Babinski appeared. There was no nuchal rigidity. Roentgenograms of the skull showed small irregular areas of decreased density in the left frontotemporal region. Roentgenograms of the chest were negative. A ventriculogram showed a left frontotemporal mass.

A craniotomy was done, and when the dura was opened a surface abscess was encountered, 5 to 10 cc. of gray odorless pus escaping. A smear of this pus showed "actinomycosis." The site was not disturbed further, but was irrigated with 100,000 units of penicillin. A burr hole was placed in the middle of the bone flap and tube drainage instituted. Ventricular needle exploration failed to reveal any more pus, and an additional 100,000 units of penicillin in 10 cc. of saline was instilled the second time. On the following day the bone flap was reopened and 2 to 3 cc. of pus encountered along the edges of a fairly firm circumscribed mass, 5 to 6 cm. in diameter, in the subcortex of the inferior aspect of the Sylvian fissure. This mass was enucleated entirely and 50,000 units of penicillin was instilled locally. Histologic examination of the mass revealed an abscess due to actinomycosis.

Systematic sulfadiazine and penicillin were continued and the patient was discharged on the 137th hospital day as cured, with slight hemiparesis and minimal speech defect. Improvement continued, and at present, eight years after the operation, she is active and well except for infrequent episodes of Jacksonian seizures and transient aphasia.

More observation is necessary before the ominous prognosis for cerebral actinomycoses can be changed, but the new therapeutic agents justify hope for a disease previously considered uniformly lethal, and undoubtedly will encourage further interest in this curious affliction. On theoretical grounds, the basis of successful treatment is already provided as demonstrated by the in vitro sensitivity both of Actinomyces bovis and Nocardia infections, and by reports of many cures in extracranial actinomycoses. Perhaps more heroic neurosurgical procedures should be employed, such as have been attempted in some cases of tuberculous meningitis, for example, drainage or excision of abscesses,

intraventricular instillation of the drugs, section of the tentorium, and Torkildsen procedure. Earlier diagnosis also may be crucial to successful treatment, and more refined laboratory analysis seems desirable, including classification of the actinomycoses into those due to Nocardia and those due to Actinomyces bovis. Sensitivity tests are certainly mandatory in the present state of contradictory evidence regarding relative sensitivity of the organisms. Most necessary is the collaborative efforts of the internist, mycologist, neurologist, and neurosurgeon.

SUMMARY

It can be stated that actinomycosis is an uncommon disease of the central nervous system, with the usual implied qualification that the diagnosis is often missed. It should be considered in the differential diagnosis of chronic obscure infection, especially if tuberculosis has been ruled out.

The fungi causing actinomycoses in man belong to two biologic types: Actinomyces bovis which is Gram-positive, anaerobic, and non-acid-fast; and Nocardia asteroides which is aerobic, Gram-positive, and partially acid-fast. Nocardia further differs from the former by being rarer and more virulent, spreads by hematogenous metastasis rather than by direct extension, and is more likely to invade the central nervous system. It is more sensitive to sulfonamides than Actinomyces bovis, while Actinomyces bovis is more sensitive to penicillin. Brain abscess and meningitis are the two common central nervous system complications.

Three fatal cases are described, with reports of two autopsies. One showed typical multiple abscesses and the rare manifestation of mycetoma due to nocardiosis. A fourth case was cured by combined chemotherapy and surgery, with an eight year follow-up period.

There is need for earlier diagnosis, prompter subclassification of the actinomycoses into those due to Actinomyces bovis and those due to Nocardia asteroides, with appropriate therapy guided by sensitivity tests. Some of the more recent studies have been reviewed, and therapeutic measures enumerated.

Grateful acknowledgment is made to the following whose work contributed to this study: Dr. William T. Spence, Dr. Ruth Wichelhausen, Dr. W. C. Emmons, Dr. J. S. Howe, and Dr. J. P. Gallagher.

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TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Management of Head Injuries

*R. C. Hardy, M.D.**

The greater use of mechanical means of transportation has resulted in an increasing occurrence of head injuries. The universal nature of the problem and the large number of victims obviates the possibility of their care exclusively by neurosurgeons. The proper management of such cases and in particular the recognition of signs indicating surgical intervention are of importance to the entire medical profession.

INITIAL EVALUATION

The initial evaluation of a patient who has sustained a head injury is exceedingly important. Comparison of this early observation with the patient's later clinical picture may indicate a course of either conservative or surgical management. A detailed history is helpful when it is available, and may rule out such causes of unconsciousness as cerebral apoplexy, drug intoxication, and diabetic coma. The duration of unconsciousness and the possible occurrence of a lucid interval are important details. The state of consciousness observed at the time of the examination should include such information as whether the patient is oriented, whether he responds to simple requests, or whether he reacts to painful stimuli.

An early record of the blood pressure, pulse rate, and character of respiratory excursions is important. With increased intracranial pressure the blood pressure may rise, the pulse rate may diminish, and respirations may become irregular or assume a Cheyne-Stokes' character.

The scalp should be examined carefully. Edema of the scalp in the temporal fossa frequently accompanies an underlying linear fracture and epidural hemorrhage. Scalp lacerations suggest the possibility of significant blood loss preceding hospitalization. These lesions constitute a source of intracranial infection, and should be carefully debrided and properly sutured. Leakage of cerebrospinal fluid and extrusion of pulpified brain from the scalp laceration are observed occasionally and indicate severe underlying damage. Contusion about the mastoid area or orbits may indicate the

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presence of a fracture at the base of the skull. Bleeding from the nose or ear may be only a manifestation of injury to the soft part, but may denote a basilar skull fracture. Discoloration of the tympanic membrane denotes a fracture of the middle fossa.

In an unconscious patient, a hemiparesis may be indicated by a difference in voluntary movements of the extremities on the two sides of the body, or by a difference in resistance to passive stretch of the muscles on the two sides. Supraorbital pressure causing facial grimacing may indicate a weakness not otherwise apparent.

Damage to any of the cranial nerves has been described in cases of head trauma, especially when the base of the skull is fractured. The third, fourth, sixth, seventh, and eighth cranial nerves are injured most frequently. The nerves tend to recover from injury, but the recovery may be incomplete.

Pupillary dilatation and fixation to light are the result of oculomotor nerve damage. A change in the state of the pupils often follows herniation of the uncus of the temporal lobe through the tentorium cerebelli. When it accompanies an intracranial hematoma, it is more often on the same side as the hematoma. Papilledema rarely becomes manifest under 24 hours, and in general it is not a frequent sign following head injuries.[1,2]

Nuchal rigidity may result from the irritating effects of blood in the cerebrospinal fluid. It may also denote a cervical spine injury.

Other injuries should be sought, particularly those of the chest, long bones, or abdominal viscera. Meredith[3] has emphasized the rare occurrence of shock with uncomplicated head injuries, and has indicated its frequent association with trauma of other parts of the body.

A roentgenographic examination should be obtained early if there are no contraindications. If the patient is in shock or is in obvious need of immediate surgical management, the x-ray study should be deferred. Roentgenograms of satisfactory technic may be of considerable diagnostic aid. Depressed fractures will be outlined. Linear fractures crossing the arterial grooves and sinuses of the skull will be demonstrated. Basilar fractures are usually difficult to define, but stereoscopic Waters views may demonstrate these lesions. If the pineal gland is calcified, a shift of its position is of considerable importance. Roentgenograms of the cervical spine should be obtained in all cases of severe head injury, since an otherwise unrecognized fracture or dislocation of a cervical vertebra is demonstrated occasionally.

The question of spinal puncture as a diagnostic procedure in head injury remains controversial. Each case should be considered on the basis of its inherent problems. The information obtained by spinal puncture in one case may be of considerable importance, while in another individual the associated dangers of the procedure might exceed its value. The Queckenstedt test of compression of the veins in the neck should not be done in patients with head injuries. It serves no useful purpose, and by increasing intracranial pressure it may favor herniation of the brain through the tentorium cerebelli or foramen magnum.

CARE OF THE UNCONSCIOUS PATIENT

With an unconscious patient, immediate consideration of the airway is imperative. Availability of oxygen may be reduced by obstruction of the respiratory passage, by accumulated secretions, or by a dependent position of the tongue against the pharynx. Labored breathing causes elevated intrathoracic venous pressure, which in turn leads to venous congestion of the brain, increased intracranial pressure, and further anoxia.

The experimental work of White and his co-workers[4,5] has shown the effects of anoxia and of increased carbon dioxide content of arterial blood in causing an increase in brain volume. The unconscious patient should be maintained on his side with the face down. This postural drainage of secretions should be supplemented by suctioning every two hours or more often if necessary. Atkins[6] and Echols and his co-workers[7] have emphasized the value of tracheotomy in patients with respiratory difficulty or in whom prolonged unconsciousness is anticipated.

Restlessness in an unconscious patient is frequently the result of a distended bladder; an indwelling catheter should be inserted early. When restlessness is the direct result of head trauma, paraldehyde or choral hydrate may be administered in judicious dosage.

The syndrome of neurogenic hyperthermia and its physiologic basis have been discussed by Erickson.[8] Temperatures in excess of 102° should be lowered by the use of alcohol sponges, aspirin by mouth or rectum, and in extreme cases by ice water enemas.

Oral hygiene is necessary for the prevention of infection of the parotid gland. Fluid requirements may be maintained by infusions during the first three days following injury. Subsequent feedings of an unconscious patient should be administered by Levine tube. Normal hydration should be maintained.

SURGICAL CONDITIONS ASSOCIATED WITH CRANIOCEREBRAL TRAUMA

Approximately 20 per cent of patients hospitalized with head injuries require surgical intervention.[9] The surgical treatment of craniocerebral trauma is concerned with the following lesions: depressed fractures of the skull, extradural hemorrhages, subdural hemorrhage, subdural hygroma, intracerebral hematoma, persistent cerebrospinal fluid otorrhea or rhinorrhea, and gunshot and missile wounds of the brain.

Depressed skull fractures are frequently recognized only by radiographic study, but x-rays often fail to show the true extent of depression. If the fracture is compound, the wound should be debrided and the depressed fragments elevated as soon as the condition of the patient permits. If the depressed segment enters the frontal sinuses, the mucous membranes of the sinuses should be exenterated. Simple depressed fractures should almost always be elevated, but the procedure is not ordinarily an emergency. The subdural space should be explored at the time the depressed fracture is elevated, due to the occasional occurrence of hematoma. The frequency of post-traumatic epilepsy increases as the site of injury approaches the motor cortex.[10,11]

Intracranial hematomas may be extradural, subdural, or intracerebral in location. The clinical picture is generally dependent upon whether the source of bleeding is arterial or venous.

Extradural hematomas are usually arterial in origin and, due to their rapid expansion, require immediate evacuation. The classic lucid interval between unconsciousness from the injury and coma due to the hemorrhage is a reliable finding, but may not occur. The change may be one from a less conscious state to a deeper one. Other signs, such as hemiparesis particularly of the face and upper extremity, dilatation of the pupil, elevated blood pressure, and bradycardia are of great importance when they occur. Munro[12] has emphasized that the neurologic findings from any one examination are not as important as the changing of neurologic signs. The high mortality rate of near 50 per cent[12–14] is due in part to associated irreversible brain damage, as well as to failure of diagnosis and delay in resorting to surgery. The under-

lying subdural space should be explored, due to the occasional concomitant occurrence of subdural hemorrhage.[15]

Extradural hematomas of the posterior fossa arise from the laceration of a dural sinus.[16,17] There is frequently a fracture of the overlying occipital bone.[16,18] Symptoms and signs are variable. Headache, nausea, staggering gait, increasing drowsiness, tilting of the head to one side, nuchal rigidity, nystagmus, and later hypotonia and a decrease in deep tendon reflexes have been noted in the cases reported.[16–20] Treatment consists of suboccipital craniotomy with removal of the clot.

Subdural hematomas are usually of venous origin. They occasionally expand rapidly due to arterial bleeding. The clot tends to accumulate over a widespread area of the convexity of a hemisphere. Organization occurs with ingrowth of fibroblasts from the dural side, resulting in membrane formation about the clot which is thicker on the dural side.[21,22] When the process of organization is less efficient, there is a greater tendency for the hematoma to become liquified and break down into smaller protein molecules. The resulting osmotic imbalance on the two sides of the arachnoid membrane is responsible for the passage of cerebrospinal fluid into the subdural space and the slow expansion of the hematoma.[23] The clinical manifestations of subdural hematoma are extremely variable, and may not become apparent until weeks or months following injury of either trivial or consequential nature. Headaches are common, and progressive mental changes often suggest a cerebral tumor or even a degenerative brain disease as the diagnosis. Convulsions are uncommon in adults,[24] but they are frequently seen in infants.[25] The electroencephalogram is rarely of diagnostic aid.[26] The surest and one of the most frequent means of recognition of subdural hematomas is visualization by surgical means. In general, patients who fail to improve or who get worse should have burr openings. Exploration of both sides of the skull is important due to the bilateral occurrence of hematomas in about 15 per cent of the cases.[27–29] When a well-defined membrane is present it should be removed, due to the possibility of hemorrhage from the sinusoidal vessels contained within it,[28] and in order to permit expansion of the depressed brain.[1]

The subdural hygroma is a collection of clear fluid in the subdural space. The fluid has been thought to enter by valve-like tears in the arachnoid membrane which prevent its return to the subarachnoid space,[30] although Munro[21] considers it to be a form of subdural hematoma. The clinical course, recognition, and treatment of the hygroma is similar to that of a subdural hematoma.

Massive hematoma within the brain substance occurs uncommonly when there has been laceration or contusion of the brain. Differentiation from epidural and subdural hemorrhage is often difficult, and arteriography or ventriculography may aid in the diagnosis. Clinical improvement follows evacuation of the hematoma.

Cerebrospinal fluid otorrhea or rhinorrhea usually ceases spontaneously within ten days. Persistent otorrhea is rare, but rhinorrhea occasionally continues with the development of a permanent fistulous tract. Examination of the fluid for sugar will aid in differentiating it from nasal secretions. A dye test may be performed by introducing indigocarmine into the lumbar subarachnoid space; a change in color of nasal fluid will make the diagnosis positive. Surgical repair of the defect is necessary to prevent infections of the meninges and brain.

The subject of pentrating head wounds has recently been considered in detail by Matson.[31] Mortality associated with

these injuries was reduced from 29 per cent in Cushing's World War I series to about 14 per cent during World War II. Thorough debridement of foreign matter and pulpified brain along the missile tract is of paramount importance. All indriven bone fragments should be removed, since they are frequently associated with abscess formation when they are retained.[32–35] The missile itself is less frequently associated with abscess formation [3,34] and should be removed only when it is accessible. Parenchymal hematomas may be encountered at any point along the missile tract and are particularly common at its distal portion.[33] Fascial grafts are necessary when a primary closure of the dura is impossible. Secondary infections usually follow inadequate debridement[33] and should be managed by radical debridement and closure without drainage.

SUMMARY

The important considerations in the initial evaluation of the patient with head trauma are reviewed. Proper care of the unconscious patient is outlined, including the importance of an open airway and of oral hygiene, the management of restlessness and hyperthermia, and the administration of fluids. The surgical conditions associated with head injury are defined, and the treatment of each is discussed.

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As a rule, the convulsion of a severe epileptic fit begins by tonic spasm, causing violent, strained distortion of head, face, and limbs.

The first evidence of the commencing spasm is, in a large number of cases, a deviation of the head and eyes to one side, or an actual rotation of the head. Sometimes the head is turned "as far as it will go," without any rotation of the trunk. Occasionally the trunk is rotated, and the patient may even turn round, once, twice, or three times, before falling. The eyes are always directed towards the side to which the patient turns. The mere deviation of the head is probably the result of the discharge being greater on one side than on the other. This is shown in certain severe fits in which a transient post-epileptic phenomenon (foot-clonus) succeeds the fit. If there is initial rotation of the head, the foot-clonus may be found only on the side towards which the head has been rotated. It is shown also by the phenomena of fits which are unilateral or begin unilaterally; the head and eyes are first turned towards the side on which the convulsion commences. The head is turned by the opposite sterno-mastoid. Each of these muscles acts in physiological association with the muscles of the limbs on the opposite side, turning the head, for instance, towards the arm which is in use. The association is of the movements, not necessarily of the muscles. In a right-sided epileptic fit the spasm involves the *left* sterno-mastoid, turning the head to the right. The lateral muscles of the eyeballs, acting together, turn both eyes towards the side affected. If the spasm, after affecting the limbs on one side, passes over the limbs on the other, lessening on the side first affected, the head and eyes are turned towards the second side when this is involved. The condition in unilateral convulsion (as Hughlings Jackson has pointed out) is always the opposite to that in unilateral paralysis. In the early stage of hemiplegia the head and eyes deviate *from* the paralyzed side in consequence of the weakness of the muscles which should turn them to that side. They thus deviate towards the side of the cerebral lesion. In the unilateral convulsion there is deviation *from* the side of the brain affected, and *towards* the limbs which are convulsed.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Charles Rupp, M.D.
and Helena E. Riggs, M.D.

CASE HISTORY

A 45 year old white male was admitted to the neurologic service of the Philadelphia General Hospital on February 18, 1943, in a delirious state. According to his friends he had had a cold and complained of pain in the chest for a week. Two days before admission he developed auditory and visual hallucinations and attempted to jump out of a window. For the previous two years he had had transient double vision which recurred several times a day, becoming persistent about three months prior to hospitalization. He had also had severe periodic headaches for a year, and his ankles had been swollen for about six months. During the previous month there had been nonprojectile vomiting with occasional hemoptysis. For about two weeks he had felt weak. He had been a heavy drinker for a number of years.

Physical examination revealed a poorly nourished man who did not appear acutely ill. Temperature was 99.4° F., blood pressure 115/90, and pulse 80. There was evidence of chronic rhinitis, the tongue was red and beefy, and there was erosion at the corners of the mouth. The lungs were normal aside from occasional rales at the bases. The heart was not enlarged, and there were no murmurs. The liver edge was palpable 1 cm. below the costal margin. There was slight tan discoloration of the dorsum of the hands, and minimal wasting of the muscles of the shoulder girdle and the interossei muscles of the hand.

On *neurologic examination*, the patient was disoriented for time and place. Mental processes were slow and his recent memory poor. The eyes were fixed in a forward position with a slight internal strabismus. The pupils reacted sluggishly to light and accommodation. There was slight ptosis of both lids, and the extraocular movements were limited in all directions. Convergence was poor. Tremors of the lips and tongue were present, and speech was slurred. All the deep tendon reflexes were diminished; there were no pathologic reflexes, but the abdominal and cremasteric reflexes were not elicited. Finger-to-nose and heel-to-knee tests revealed tremors bilaterally. The gait was staggering. Pain was elicited when the calf muscles were squeezed. Position and vibratory senses were lost in the lower extremities and there was hyperesthesia to touch and pain in the legs.

Laboratory studies: hemoglobin 10.5 gm.; red cell count 3,300,000; white cell count 5,000; normal differential. Urine analysis revealed a trace of albumin and occasional hyaline casts. The blood serology was negative, and the blood sugar and blood urea nitrogen were within normal limits. Lumbar puncture revealed an initial pressure of 110 mm. of water; there were no cells; protein was 50 mg. per cent. Spinal fluid serology and colloidal gold tests were negative.

The patient developed fluid in the abdomen, had two episodes of hemoptysis, gradually became comatose, and died four days later on February 21, 1943.

From the neurologic services and laboratory of neuropathology, Philadelphia General Hospital, Philadelphia.

CLINICAL DISCUSSION

DR. CHARLES RUPP (Visiting chief in neurology): On admission this man was disoriented and had memory disturbances. His speech was slurred and his gait staggering. All of these symptoms occurred a few days after he developed an acute respiratory infection. He had been a chronic alcoholic for many years. There was deep muscle tenderness, the deep tendon reflexes were diminished, position and vibratory senses were disturbed, and wasting of the hand muscles was present. These neurologic and psychiatric findings are consistent with a diagnosis of chronic alcoholism complicated by alcoholic polyneuropathy.

The poor nutritional state, red beefy tongue, erosion about the mouth, attacks of hemoptysis, and a palpable liver suggest that he also had cirrhosis of the liver with an associated deficiency of the B vitamin group.

Of particular neurologic interest are the ocular muscle findings. The patient had transient diplopia for two years which became permanent three months before admission. There was slight ptosis of the lids, an internal strabismus, and all extraocular muscle movements were limited. These findings suggest a lesion localized in the brain stem in the area of the third, fourth, and sixth cranial nerve nuclei.

Myasthenia gravis should be considered in the differential diagnosis, but the long duration of symptoms without involvement of the lower cranial nerves and the ultimate permanency of the extraocular muscle symptoms do not support this diagnosis. In myasthenia gravis, the symptoms are usually fluctuating and the deep tendon reflexes are not absent. There are no sensory disturbances.

Extraocular palsies are not infrequently the first manifestation of pontile tumors and they may be intermittent, but the long duration of symptoms with the absence of involvement of the long tracts and other cranial nerves such as the seventh make this diagnosis unlikely.

A diagnosis of multiple sclerosis has been suggested. In favor of this is the transitory nature of the diplopia and evidence of cerebellar involvement, but there was no pyramidal tract involvement, visual or sphincter disturbances, all of which would be expected in a case of multiple sclerosis of two years' duration.

The possibility of Wilson's disease has also been considered. In favor of this is the presence of liver cirrhosis and the tremors. However, this patient's tremors were inconstant and of the intention type; there were no disturbances of muscle tone, and the reflexes were diminished rather than increased. No Kayser-Fleischer ring was observed. Extraocular palsies are not characteristic of this condition.

There remains the diagnosis of Wernicke's polioencephalopathy. Involvement of the extraocular cranial nerve nuclei is common in this condition. In the early stages pathologic findings may be reversible, and this would account for the transitory nature of the diplopia. The patient was a known alcoholic and showed signs of alcoholic psychosis, polyneuropathy, and avitaminosis. This disorder is thought to be due to a deficiency of the B vitamin complex, especially thiamin, and is often associated with a psychosis and polyneuropathy. I believe the whole clinical picture can be summarized as Wernicke's polioencephalopathy associated with an alcoholic psychosis, polyneuropathy, gastritis, and cirrhosis of the liver.

PATHOLOGIC DISCUSSION

DR. HELENA RIGGS (Neuropathologist): At necropsy there was advanced fatty cirrhosis of the liver, atrophic gastritis, and esophageal varices. There were symmetrical lesions in the brain localized

to the paraventricular nuclei of the hypothalamus, the mammillary bodies, the periaqueductal gray matter, the sixth nerve nucleus in the pons, and the dorsal vagal nucleus in the medulla. In these areas the vessels were dilated, tortuous, and showed endothelial proliferation with red cells and occasional lymphocytes in the perivascular spaces. Proliferation of astrocytes and microglia were present in these areas.

Diagnosis: Wernicke's disease.

RESIDENT'S QUESTION: What is the most common feature of Wernicke's disease?

DR. RIGGS: In the cases reported from this hospital, the most constant finding was psychosis. We investigated 42 cases between 1934 and 1943 for which the diagnosis was made at necropsy. These patients came into the hospital very ill with psychosis, convulsions, or coma as the outstanding feature. Extraocular palsies were either overlooked or were not very conspicuous. Although the original description of the condition mentions ophthalmoplegia, this finding was present in only five of our cases. Isolated extraocular palsies occurred in five others. Ataxia of either limbs or speech was fairly common. The usual picture in Wernicke's disease is that of a patient who has a long-standing nutritional deficiency, which may not necessarily be due to alcohol, develops an intercurrent infection or a gastrointestinal disorder associated with prolonged vomiting during which he becomes psychotic, and may, in addition, show tremors and one or more ocular palsies.

DR. RUPP: How common is cerebellar involvement in Wernicke's disease?

DR. RIGGS: The cerebellum itself is infrequently involved, but lesions are often found in the vestibular and inferior olivary nuclei.

DR. RUPP: Since this condition has become better known, have you observed more cases?

DR. RIGGS: There were 42 cases in the decade 1934 to 1943, and only 13 from 1944 to 1953. This is good evidence for the actual decrease in the frequency of the condition, since these figures are based on necropsy findings rather than the clinical diagnosis. Apparently, the general public has become more "vitamin conscious."

RESIDENT: Do you think the heavier consumption of alcohol in the 1930's may partially account for the large number of cases at that time?

DR. RIGGS: I do not believe that alcohol is the prime offender in these cases. It is more a deficiency disease. Many cases came from the tuberculosis service and the gynecologic wards where infection superimposed on poor diet seemed to be the chief factor. The best evidence against an alcoholic etiology was the fact that the greater number were negro females under 40 years. If alcohol had been the major factor, we would have expected more cases among older males. According to government surveys, it is the young negro females who have the poorest diet. In this hospital, Wernicke's disease appears to develop more as a complication of organic disease rather than as a result of alcoholism.

DR. RUPP: I might add that some years ago we saw a number of cases of Wernicke's disease on the obstetric service. All were individuals in a border line state of nutrition who remained asymptomatic until they became pregnant. With the increased metabolic requirements of pregnancy, they developed Wernicke's disease.

RESIDENT: What is the relation of Wernicke's syndrome to Korsakoff's psychosis?

DR. RIGGS: Korsakoff's psychosis may be associated clinically, but an uncomplicated Korsakoff's psychosis shows none of the characteristic pathologic changes associated with Wernicke's disease.

DR. RUPP: What areas of the brain are most frequently involved in Wernicke's disease?

DR. RIGGS: For a list of the areas involved in our 42 cases, I would refer you to the original paper.[1] Most commonly, however, the disease involves the mammillary bodies, the region around the ventricles in the hypothalamus, the aqueduct, and the fourth ventricle. Any area of the brain including the cortex may be involved. The pathologic changes of themselves are not specific, but the symmetrical location around the ventricular system is characteristic.

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As the suffering in megrim is greatly aggravated by every form of motion and muscular exertion, as well as by sensorial impressions of all kinds, and, on the other hand, is relieved by recumbency and quiet, the patient from the first commencement of an attack should retire to a darkened room, as free from noise and disturbance as possible, and lying down endeavor to maintain whatever position appears at first most comfortable. If by this means he should also succeed in getting to sleep the attack will often be shortened, and in any case the suffering will be less than it would have been had he persevered in remaining about. Dr. Heberden says on this point, "Nec invenire potui quibus remediis sanetur, aut etiam leniatur; nisi quod cubanti in lecto dolor citius finitur, et impetus ejus aliquantum minuitur." Professor Lebert recommends that the position should be a slight incline with the head highest. My own opinion is that fixity and the absence of all effort are the most important considerations; but if the vessels of the head are relaxed and throbbing, it may be desirable to adopt the Professor's suggestion. If there is chilliness and the feet are cold, a hot bottle and blankets will be required.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Neurology BOOK REVIEWS

Diseases of Muscles: A Study in Pathology

Raymond D. Adams, M.D., D. Denny-Brown, M.D. and Carl M. Pearson, M.D. 1953. New York: Paul B. Hoeber, Inc. 556 pages. $16.00.

This monograph, according to the authors, was originally planned as a syllabus of the pathologic changes in skeletal muscle to aid in the teaching of graduate students of neurology and pathology. In reviewing the literature of the subject, however, the project assumed proportions far greater than had been anticipated, and as a consequence this systematic account of muscle disease has materialized.

Diseases of Muscle is a thorough and painstaking study of normal skeletal muscle and the changes that take place in disease. It is beautifully printed, and several hundred superb microphotographs illuminate the text and form a valuable atlas of the pathology of muscle. The book is divided into three major sections. It opens with a detailed discussion of the normal structure and function of muscle, dealing comprehensively with embryology and histology and including innervation and blood supply. The biochemistry of muscle, however, and physiology of muscular contraction and neuronal activity are dealt with in less detail. The second section considers pathologic changes of skeletal muscle, including both experimental pathology and the general reactions of human muscle to disease. The last section, comprising more than half of the book, deals with various pathologic entities of muscle disease, including congenital defects, the dystrophies, myositis, muscle tumors, traumatic and circulatory diseases, the spinal and neural atrophies, and miscellaneous conditions including toxic, metabolic and endocrine diseases, and disorders of excitability and contractility. There is, in conclusion, a brief chapter on differential diagnosis and methods of pathologic study.

As far as is known, there is no other exhaustive treatise on diseases of muscle in the English language, and this book therefore fills a conspicuous gap in the medical literature. Many of the diseases mentioned are mainly within the realm of the neurologist, but the orthopedist, the internist, and the pathologist as well can gain much help from the book. The authors have made a specialty of muscle pathology, a field that is often overlooked by both neuropathologists and general pathologists.

The reviewer has but two general criticisms to make. In the first place, it seems that the biochemistry and physiology of muscular contraction, including the newer aspects of the electrophysiology of muscle, are given less stress than they should in view of present-day approaches to disease of muscle. And in the second place, the discussion of specific diseases could be more impressive if more stress were placed on clinical

presentations and less on controversy from the literature regarding etiology and pathophysiology. Both of these criticisms are perhaps negated, however, when one recalls that the subtitle of the book is *A Study of Pathology*.

This book must be considered more a reference work on muscle disease than a clinical presentation of such disease. Nevertheless, it is a most worthwhile, comprehensive, and timely study which must be regarded as an exceedingly important contribution to medical literature.

R. N. DE J.

Poliomyelitis

Volume I. Papers and discussions presented at the First International Poliomyelitis Conference. 1949. Philadelphia: J. B. Lippincott Company. 360 pages, $5.00.

Volume II. Papers and discussions presented at the Second International Poliomyelitis Conference. 1952. Philadelphia: J. B. Lippincott Company. 555 pages, $7.50.

These two handsome achievements of the publishing industry are collections of papers presented at the First and Second International Poliomyelitis Congresses in New York City (1948) and Copenhagen (1952). The volume relating to the Second International Poliomyelitis Conference includes 158 pages of beautifully illustrated representations of the scientific exhibits which were on view.

The first volume includes 20 original papers from the 1948 Congress, which are grouped under several general headings covering the economic and epidemiologic importance of poliomyelitis, problems of pathogenesis, the management of the various stages of the acute diseases, and the rehabilitation of the residual disabilities. The treatment of bulbar poliomyelitis is discussed at some length, and the immunology, therapy, and public health aspects of epidemic poliomyelitis are considered. Each section is followed by a discussion by the participants, as well as open discussion from the floor. The same general format is followed in the second volume, which is, however, broken down into four symposia concerning the virus, differential diagnosis, the problems of immunity and resistence in poliomyelitis, and related viral infections. There is a review of the pathology and pathophysiology, as well as reviews of treatment and the ecological aspects of poliomyelitis.

As can be surmised from simple listing of the material covered, these two volumes attempt a broad coverage of the whole field of poliomyelitis. There are, understandably, some differences of opinion regarding the management of bulbar poliomyelitis, as well as some variations in the technics of rehabilitation of the poliomyelitis victim.

It is of some interest to this reviewer that neurologic representation is rather sparse and the majority of the articles are by laboratory men, orthopedists, and pediatricians. Any neurologist will find most interest in the fact that perusal of these volumes will bring him up to date in the more recent advances in virus studies and epidemologic problems. However, nowhere will the reader find any discussion of the most recent and perhaps most important development, the protective use of gamma globulin.

The publishers are to be congratulated upon the excellent format, the printing, and reproductions which these two volumes present.

A. L. D.

Physiological Foundations of Neurology and Psychiatry

Ernst Gellhorn, M.D., Ph.D. 1953. Minneapolis: University of Minnesota Press. 556 pages. $8.50.

In the preface to this book, the author states that his aim is to present, "by no means all, but only some physiological foundations of neuropsychiatry . . . . those with which the writer is familiar through his own experimental work." Despite this modestly stated aim, the book covers almost all of the field of neurophysiology that bears on the practice of neurology and psychiatry. The discussion of all topics is based on experimental evidence. The details of the experimental work of Gellhorn and of a host of other workers in this field are presented lucidly, a unique feature of the book being an attempt to connect all of the experimental material by a theoretical synthesis. This method of presentation has obvious strengths and weaknesses, but does give one a stimulating experience in reading the book, whether or not one agrees with the interpretation of the material. Who could, in the present state of our incomplete knowledge of this field, agree with all of the postulates put forth by the author?

Despite the theoretical framework in which the book is couched, the actual reporting of the experimental work is always kept separate from the theoretical interpretations. This results in an excellent reference source on experimental work in this field. Particularly well done and complete is the review of recent experimental work relative to the autonomic nervous system. Here for the first time the more recent work relative to epinephrine and nor-epinephrine and emotions is brought within the covers of a book. Almost no references are made to the recent physiological work relating to operations on the frontal lobe.

The work is divided into six parts, the first three parts covering material which is mostly in the province of classical neurology, that is, factors relative to the neuromuscular system and consciousness. The latter three parts of the book deal with autonomic physiology, integrations, and applications. The section on applications refers almost entirely to psychiatry, with particular reference to the shock therapies and carbon dioxide treatment. The reviewer does not feel competent to comment on the last chapter in the book, which deals with some of his own work.

One would have many reservations about the conclusions reached about the modus operandi of the various shock therapies. The chapter on the physiological foundations of carbon dioxide treatment is the weakest in the book, as there is considerable doubt in the minds of many that the effect of carbon dioxide as used in treatment of neuroses is based on any other factor than suggestion.

The book is handsomely printed, contains 556 pages, with an excellent bibliography of some 1,263 references. A complete index makes the volume easy to use.

The book is one of the best compendiums of neurophysiology as related to neurologic and psychiatric practice that the reviewer has seen. It is certainly the most provocative and stimulating to read due to the many suggestions and interpretations of the material put forth by Dr. Gellhorn. However, these theoretical formulations badly need experimental validation or rejection. They are, however, always carefully labelled as such and do not interfere with the use of the book as a reference work.

D. H. F.

Pain Sensations and Reactions

James D. Hardy, Ph.D., Harold G. Wolff, M.D., and Helen Goodell, B.S. 1952. Baltimore: The Williams and Wilkins Company. 435 pages. $6.50.

According to the authors, this monograph was originally intended to present in one volume the results of their collaborative investigations on pain over a period of 13 years. The scope of the book was broadened, however, to bring out a more rounded concept of the entire subject of pain sensation and reaction. The experimental work of the authors is well known to all clinical neurologists, and it is indeed helpful to have their outstanding contributions published in a single volume. These include their work on the anatomy and physiology of structures subserving pain; the study of pain thresholds, including the use of the dolorimeter; measurements of pain intensity and the "dol" scale; reactions to pain; the effect of analgesics and cerebral damage upon the pain threshold; and reactions to pain.

This book is more than a study of the anatomy, physiology, and physical aspects of pain, however. It is also a psychological treatise on the various concepts concerning pain, both the traditional concepts and the newer data regarding the phenomenology of pain. Pain is not only a sensation, but also an experience linked with strong emotions, feelings and behavior patterns. The conscious and the unconscious reactions to noxious stimulation are intimately interwoven. Thus this monograph crosses the lines of various scientific disciplines from physics through psychology and physiology to medicine, neurology and psychiatry.

R. N. DE J.

The Anatomy of the Autonomic Nervous System

G. A. G. Mitchell, O.B.E., T.D., M.B., Ch.M., D.Sc. With a foreword by Sir James Learmonth. 1953. Baltimore: Williams & Wilkins Company. 356 pages. $10.00.

This volume, prepared by the professor of anatomy in the University of Manchester, England, is a specialized one and limits itself to a discussion of the structure of the autonomic nervous system in its peripheral aspects and with its central nervous system relations. It is very well printed. There are many new photomicrographs and drawings, all beautifully reproduced.

For the teacher of the subject and the research worker, a number of opinions of a controversial order are set forth by the author with a certain firmness and challenge, and will be a source of stimulation and interest. One such topic is his placing of sensory components as an integral part of the autonomic nervous system. This would be a good subject for a seminar debate; to the reviewer it is regarded as a verbal problem, with its main point carried when the author recognizes the importance of visceral afferent mechanisms.

For those whose principal interest is in the morphology of the autonomic nervous system, this book may be recommended as an excellent supplement to other literature in the field.

A. R. V.

The Biology of Mental Health and Disease

The Twenty-seventh Annual Conference of the Milbank Memorial Fund, with a foreword by Stanley Cobb, M.D. 1952. New York: Paul B. Hoeber, Inc. 652 pages. $10.00.

This symposium, presenting the deliberations at the twenty-seventh annual conference of the Milbank Memorial Fund, should be of special interest to all neurologists, for it deals with one of the very important problems of their field of specialization – the multiple biologic aspects of mental health and disease. The 108 participants included anatomists, physiologists, geneticists, chemists, neuropathologists, neurologists, neurosurgeons, psychologists, and psychiatrists. The emphasis was placed on "basic" aspects of mental disease, and the majority of the discussants were men more interested in laboratory investigation than in the clinical fields. Of the principal speakers, ten were chemists, six were physiologists, five psychiatrists, four neuropathologists, three anatomists, three psychologists, two geneticists, and one internist.

In an attempt to obtain a comprehensive view of the subject, representatives of all disciplines were brought together and given the opportunity to cover it in full scope. The aim was to have the members of each discipline become acquainted with the progress and future plans of other fields. This, it was hoped, would widen the horizon of each discipline and encourage the application of combined technics.

The biology of normal mental activity is the subject of the first half of the symposium. Cerebral structure is viewed both in its histologic and chemical aspects, along with discussions of cerebral circulation, the blood-brain barrier, organic and inorganic metabolism of the brain, the electrical activity of the neurons and of cerebral integration, patterns of cerebral localization, the endocrine influence on personality and behavior, and the contribution of genetic endowment to mental performance.

The second half of the book is devoted to mental disorders, both clinical and experimental. The etiology and morbid alterations of disease states are presented, as well as the structural and functional changes of induced disorders. Among the latter are the abnormal reactions to drugs, hypoxia, starvation, avitaminosis, and conditioning. The sections on mental deficiency, mongolism, metabolic and physiologic disturbances in the psychoses, enzymatic changes in mental disease, and the histopathology of psychoses of unknown origin are of special interest to the clinical neurologist. Considerable attention is given to biochemotherapy, including hypoglycemic coma, Metrazol and electroshock, carbon dioxide inhalation, and preliminary reports on the effectiveness of niacin in the treatment of depressive states, and of ACTH and cortisone in the depressive and schizophrenic psychoses.

The presentations, as in all symposia of this type, are uneven. In spite of the attempt to bring in all disciplines, many important ones are missing. There is certainly diversity of opinion, as there should be, and there are often disagreements. As Dr. Cobb states in his foreword, however, many of the latter were the result of semantic difficulties. This book is a stimulating one, and the planners of the symposium are to be congratulated on their judgment and choice, not only of subjects but also of participants. If this book serves no other purpose, it will be of permanent value as a source book and as an important step toward further investigation of the biologic aspects of mental disease. R. N. DE J.

Clinical Neurology

Frank A. Elliott, M.B., Ch.B., F.R.C.P., Brodie Hughes, Ch.M., F.R.C.S., and J. W. Aldren Turner, M.A., D.M., F.R.C.P. 1953. New York: Paul B. Hoeber, Inc. 751 pages. $5.00.

This new textbook, by two competent English neurologists and the professor of neurosurgery at the University of Birmingham, is designed for the postgraduate student of medicine rather than for the junior student or the specialist in neurology. With the object in view, an attempt has been made to present the more common neurologic conditions for review and avoid the rare diseases as well as controversial methods of treatment.

The book is divided into two sections. The first, comprising a little less than a third of the volume, deals with the principles of neurologic diagnosis, although some chapters take up specific clinical entities such as epilepsy, syndromes characterized by pain, and mental disorders in organic disease. Other chapters deal with disorders of the motor system, somatic sensation, disorders of language and speech, the cranial nerves, the vegetative nervous system, and methods of examination. In all, clinical phenomena are explained in terms of anatomy, physiology, and pathology.

The second section is entitled "Systematic Neurology," and covers the more frequently encountered diseases of the nervous system. The clinical descriptions are succinct but adequate. Therapy is very briefly discussed in most instances, but the essentials of current methods of treatment are comprehensively listed. Dr. Elliott states, in his introduction, "The brevity of some of the sections on treatment will do much to sustain the charge of therapeutic nihilism which is so often levelled at neurologists, but I feel that there is nothing to be gained by the continued advocacy of ineffective nostrums. Specific measures of established value, on the other hand, have been described in full."

Many disease entities important to both the neurologist and the internist seem to be discussed somewhat too briefly and superficially, whereas the chapter on intracranial neoplasms, ably written by the neurosurgeon, is quite detailed and comprehensive. One might wish, for the benefit of the postgraduate student of medicine, to whom the book is directed, that the nonsurgical conditions as well as the neurologic complications of visceral disease had been given more attention.

The reader cannot but feel, however, on reading this book, that the authors have a wide background of excellent experience which they are admirably able to convey to others. The volume is well written; the material is attractively presented, although illustrations are few; the format is pleasing. This is another of the outstanding contributions of the British school of neurology, and will certainly find a place as a textbook in the United States. As a final, though perhaps irrelevant comment, the reviewer would like to express the wish that American books of equal value and size could be marketed at an equally low price!

R. N. DE J.

Neurology

Variability of the Course of the Guillain-Barré Syndrome

Benjamin Boshes, M.D.
and Irving C. Sherman, M.D.

In 1916 Guillain, Barré, and Strohl[1] described a syndrome of paralysis of peripheral musculature which pursued a benign course ending in recovery. Since then many articles have been written to define the limits and nature of the entity. Guillain[2] restated his position in 1936, insisting that his type of polyradicular neuritis could be identified by two important features, a protein content in the spinal fluid of 1 to 2 gm. ("cases with slight hyperalbuminosis, with an albuminoid content of from 0.3 to 0.4 gm., do not belong to the syndrome or must be regarded as instances of the abortive form") and clinical recovery in all cases. During the ensuing years numerous authors have reported instances with fatal outcome. Others described cases in which the spinal fluid protein either remained low or rose later to significantly high levels from an originally low figure and still others reported cases in which there was some pleocytosis. Guillain's rigid criteria were dropped when he retracted his original opinion in 1938,[3] agreeing that the disease could be fatal and that the protein did not always have to be so high, and Barré concurred.[4] At this time they extended the syndrome to include three other forms in addition to the simple spinal form: mixed mesencephalic, pure mesencephalic, and spinal types.

From department of nervous and mental diseases, Northwestern University, and the division of neuropsychiatry, Michael Reese Hospital, Chicago.

Read at the fifth annual meeting of the American Academy of Neurology, Chicago, April 11, 1953.

In an effort to bridge the gap between the original description of the syndrome and the additional types of cases reported, Brown and Baker[5] classified the disease into five clinical forms: abortive or mononeuritic, polyneuritic, myelitic, bulbar, and cerebral types. Further efforts at classification were made by others who attempted to differentiate Landry's paralysis from the Guillain-Barré syndrome. However, Lewy[6] claimed that this separation was artificial and based on a variability of course or severity.

Lewy's position was supported in 1949 by Haymaker and Kernohan in an excellent article entitled "The Landry-Guillain-Barré Syndrome."[7] They presented an exhaustive and critical review of the literature on both subjects and set down the clinical and pathologic findings in 50 fatal cases of their own. It was their conclusion that the disorders variously referred to as Guillain-Barré syndrome, acute infectious polyneuritis, Landry's paralysis, and others all fell into a single category. They elected to use the eponymic term, Landry-Guillain-Barré syndrome, and expressed what seems to be a logical concept of this disease in the following terms: "The disorder is characterized by a polyradiculo-neuropathy which may begin in any peripheral neurons, spinal or cranial, circumscribed or widespread; may affect predominantly the motor or the sensory neurons, or both to the same degree; it may remain essentially a radicular disorder or, according to some authors, it may extend into the central nervous system at any point, and either ascend or descend, the outcome usually being dependent on the degree of involvement of respiratory or cardiac nerves. Changes in the amount of protein and the number of cells in the spinal fluid are regarded as incidental to the disorder."

Just as the distribution of pathology may be widespread and variable, so may the course of the disease vary from case to case. The usual picture is that of an acute or subacute onset of weakness with paresthesias or sensory loss. This may progress for a few days or few weeks. A fatal termination is not uncommon. Generally, if the patient survives, there is a gradual resolution with or without residues.[8] This has led to the general belief that the patient is out of danger once evidence of recovery appears. Recent experience has taught that this is not so. In most reviews one will find reference to an occasional case which began to recover and even showed substantial return of function, only to relapse. This occurred in one of Guillain's cases[2] who developed an intercurrent infection. Roseman and Aring,[9] too, have pointed out that occasionally the disease is considered to be at a standstill when a sudden and rapid progression occurs. Such a case is also found in Baker's series of 33 cases. However, in a later article, Brown and Baker[5] state that once begun improvement continues uninterrupted, and repeated relapses should make one uneasy about the accuracy of the diagnosis. Similar relapsing cases were included in the series of Haymaker and Kernohan,[7] Hand and Rudoy,[10] Furtado,[11] and DiFiore.[12] Commenting on Furado's paper, MacKay[13] mentioned that he observed one partially remittent case in which the patient died in severe relapse, and another in which recovery from the first attack was followed over a year later by a severe but nonfatal recurrence. Furtado made

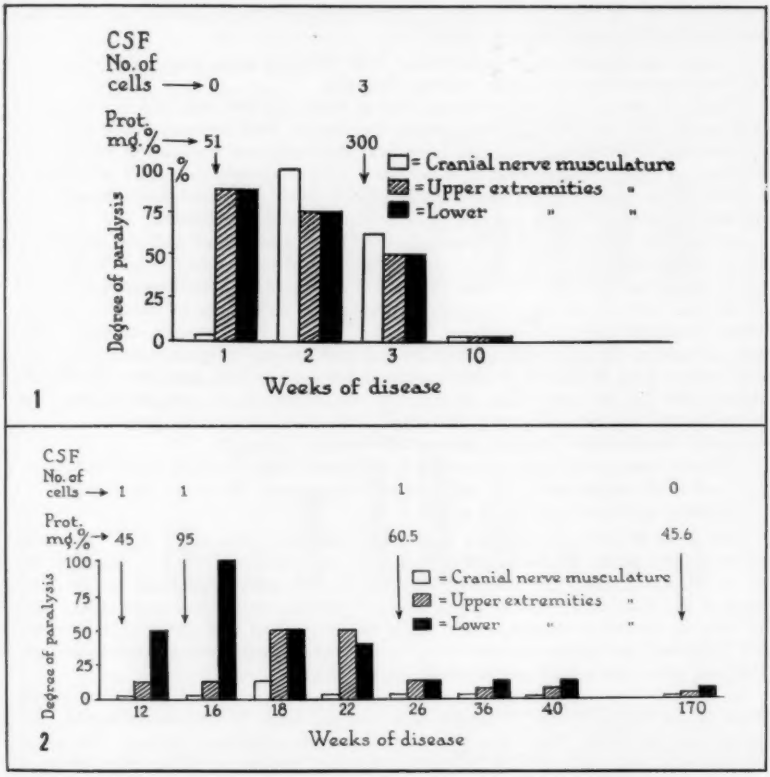

FIG. 1. Course of illness as represented by development and recession of weakness in case 1.
FIG. 2. Course of illness as represented by development and recession of weakness in case 2.

specific reference to the intermittent form of this syndrome, suggesting that the reaction in the spinal fluid is typical of serous inflammation whether of allergic or some other origin. He concluded that the features of the syndrome suggest that it might well be a peripheral form of neuro-allergy.

Despite numerous cases to the contrary, the popular misconception persists that Guillain-Barré's syndrome is a benign disease which runs a smooth course of varying speed toward recovery. We should like to emphasize the variability of the course of illness. Four representative cases illustrating the usual and exceptional courses are presented. Close study of the disease in individual cases utilizing recent laboratory technics helps throw light on factors which may be operative in the production of this variability. Development and recession of paralysis is represented graphically in the illustrations.

CASE REPORTS

Acute onset with prompt recovery (figure 1).

Rapid development of a quadriparesis with bilateral facial palsy. Recovery occurred in about ten weeks and was complete.

Case 1.—A 46 year old factory foreman had an illness in 1948 diagnosed as encephalitis which produced a transient left hemiparesis. On June 4, 1952 he noticed that his knees were buckling under him. Forty-eight hours later there appeared weakness of his left arm and later his right. Within three days he had a marked quadriparesis with preservation of all the deep and superficial reflexes. On June 8, 1952, the spinal fluid contained no cells and a protein of 51 mg. per cent. The gold curve read 1111000000.

By June 10, 1952 the achilles and patellar reflexes were absent and the other deep reflexes disappeared shortly afterwards. There was bilateral facial weakness and Kernig and Lasègue signs were present. The next day he had a severe headache. Speech was slurred and his face and jaws ached. However, the extremities had begun to move despite the absence of all the deep tendon reflexes. By June 12 there was increased strength in the upper extremities, although both sides of the face had become completely paralyzed. The spinal fluid on June 16 showed no cells, protein of 300 mg. per cent, gold curve 000001110, chlorides 654 mg. per cent, sugar 70 mg. per cent. There was a progressive return of function so that after several weeks, all evidence of the disease had disappeared.

Progressive development – gradual recovery with residue (figure 2).

Slow progression of a flaccid paralysis of the lower extremities with some weakness of the upper extremities and face over a period of 16 weeks. Resolution gradual and incomplete at 40 weeks.

Case 2.—A 64 year old housewife experienced girdle-like pain in the upper abdomen, pain in the toes of the left foot, weakness and loss of sensation in the feet, worse on the left, in September 1945. By mid-December she showed marked weakness of the distal portion of the lower extremities, absent achilles and patellar reflexes, loss of joint and vibration sense in the lower extremities, and vagus loss to pinprick and cotton-touch over the feet. There was no bladder or bowel control. The spinal fluid showed 1 cell, a flat colloidal gold curve, and a total protein of 45 mg. per cent.

In January 1946 she developed ataxia of the upper extremities, with loss of stretch reflexes except for the triceps. Vibration sense was lost from T4 down and pinprick perception from T7 down. There was left wrist drop with interosseus atrophy. The spinal fluid showed 1 cell, gold curve 1122300000, and a total protein of 95 mg. per cent. Root pains persisted chiefly over the chest. As the left hand became weaker, the foot drop improved. Bladder and bowel control returned.

In early February she could support her feet and legs against gravity. Joint sense remained absent in both lower extremities. There was spotty diminution to pinprick in a girdle zone from T3 to T12 on the left. By the end of February she was able to sit up and could perform all hand movements, although atrophy of the interossei persisted. The spinal fluid showed 1 cell, a flat gold curve, and a total protein of 60.5 mg. per cent.

By May 1946 she could perform all movements of the limbs, but the achilles and patellar reflexes remained absent. The biceps reflexes were brisk. The triceps, radial, and ulnar periosteal reflexes were diminished. Joint and vibration sense were lost in the lower extremities. Eventually the patient made a good functional recovery with only some weakness in the hands and lower extremities. Spinal fluid examination three years later showed no cells, a flat gold curve, and a total protein of 45.6 mg. per cent.

Relapsing course (figure 3).

Development of quadriplegia with bilateral facial paralysis and intercostal paralysis over a period of seven weeks. Gradual improvement during the next 14 weeks. Sudden recurrence of quadriplegia, respiratory paralysis, and facial paralysis with a "chicken-pox like" illness. Later gradual remission.

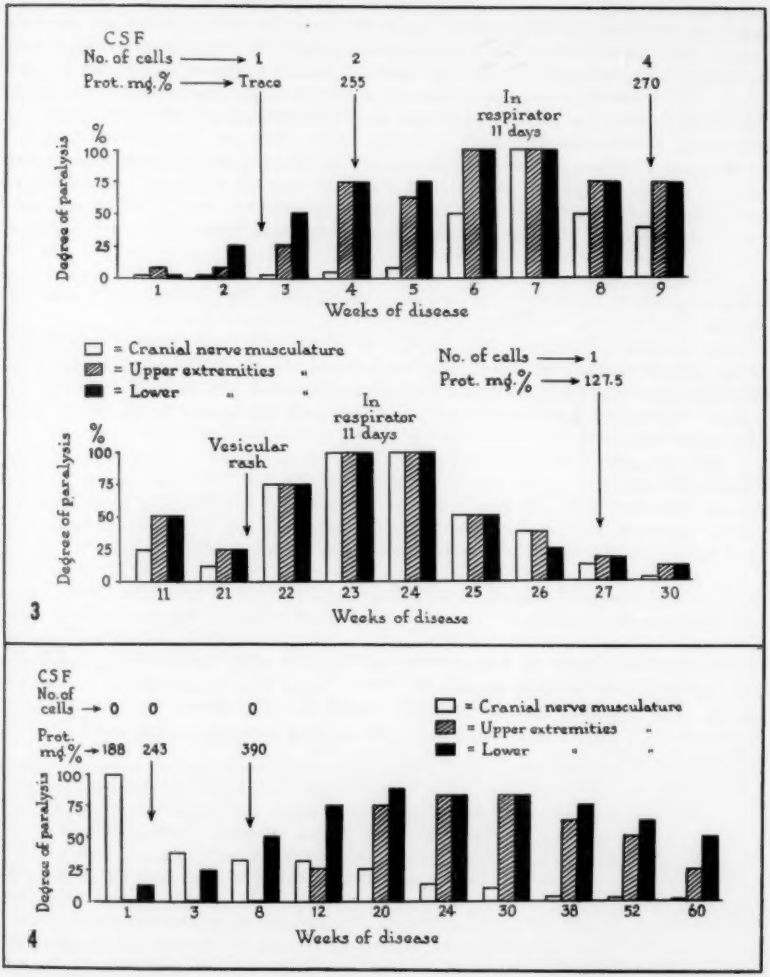

FIG. 3. Course of illness as represented by development and recession of weakness in case 3.
FIG. 4. Course of illness as represented by development and recession of weakness in case 4.

Case 3.—A 45 year old man suffered an attack of "flu" in December 1950 and again in March 1951. On April 7, 1951 he noted numbness in the tip of the little finger of the right hand. Seven days later his feet and hands were numb, weak, and clumsy. This was accompanied by pain and tenderness in the calf muscles. Examination revealed an ataxic gait, tremor of the hands, absent achilles, patellar, biceps, and triceps reflexes. There were no

pathologic reflexes. Sensation was intact. The spinal fluid showed 1 cell, a trace of protein, and gold curve of 0000011100.

By April 21, 1951 the limbs were much weaker and all modalities of sensation were diminished over the hands and feet. By April 30, 1951 he could not flex his head against gravity. There was loss of rectal awareness. All sensation was not absent below the clavicles. The spinal fluid showed 2 cells, a gold curve of 0001111000, and a total protein of 255 mg. per cent.

On May 2, 1951 sensation began to return to the lower extremities. However, within the next four days he lost all movements of the extremities and developed a bilateral facial paralysis. His chest ached and all muscles were very tender. He had to be kept in a respirator for 11 days. During this time he had a mild consolidation of the left lung base, and was confused and hallucinated for five days.

On May 26 muscle power began to return, preceded by twitching and cramps of the affected muscles. The spinal fluid on June 5 contained 4 cells and 270 mg. per cent of protein.

Improvement came slowly. The weakness of the hands and feet persisted with atrophy of the affected muscles. All deep reflexes were absent. Deep sensibility was absent in the feet and hands. Pinprick and cotton touch were diminished over the periphery and improved as one proceeded centrally. In July he gradually sat up and by August he could take a few steps.

On September 12 he began to feel sick again. He developed a scattered monolocular generalized vesicular eruption which looked like chicken-pox. The patient was growing weaker. On September 14 he lost his voice, could not bring up saliva, and became quadriplegic. There was no nuchal rigidity. Bouts of cyanosis developed, apparently from bronchial or tracheal obstruction. He was placed in the respirator where he spent 11 stormy days. Survival did not seem likely, and it appeared that if he did recover, the brain damage from anoxia would leave only a vegetating organism. Yet on September 25 the swallowing reflex returned suddenly and he coughed out the tracheal catheter. Within hours movement began to return to the limbs, and after five more days he was the strongest he had been in five months. By October 9 he had begun to walk. Recovery progressed rapidly. He left the hospital on October 25, 1951, using a cane on one side and steadying himself on a supporting arm on the other. Spinal fluid on October 11, 1951 contained 1 cell and 127.5 mg. per cent total protein. He returned to work in a few weeks.

Concomitant recovery and progression (figure 4).

> Abrupt onset of facial paralysis, first involving one side and then the other. As these recovered there was progressive loss of motor and sensory functions of the lower and then the upper extremities over a period of about six months. Since that time there has been gradual but incomplete restoration of function.

Case 4.—A 50 year old merchant experienced intense low back pain on January 18, 1952. On January 23 he noticed weakness on the right side of his face, and within the next two days it became completely paralyzed. The left side of the face was also beginning to weaken. There was some difficulty in walking because of weakness of the proximal muscles. Power below the knees and in the upper extremities was normal. The muscle stretch reflexes in the upper extremities were normal, while those in the lower extremities were absent. Sensation was intact for all modalities. Sphincter function was normal. The spinal fluid on January 25, 1952 contained 3 fresh red blood cells, no white blood cells, and 188 mg. per cent of protein.

Within four days he had developed a bilateral facial paralysis. Three days later the spinal fluid contained no cells and 243 mg. per cent protein. By February 20, 1952 he had complete recovery of the right side of his face, with slight recovery on the left, and apparent progression of weakness of the pelvic girdle. The legs and upper extremities were normal.

Within the next two months there was definite weakness of both lower extremities including the muscles below the knees. Weakness of the arms appeared with numbness of the feet. Vibration was defective from the iliac crests downward and position sense was lost in the toes. Sensation for pinprick and cotton touch was intact. The spinal fluid at this time contained no cells and 390 mg. per cent of protein.

There was a slow but definite recovery of the face with a minimal residue of weakness and contracture around the mouth on the left side. In the meantime during May, June, and July the lower extremities became worse. In May weakness became worse in the upper extremities and was quite severe in June. There was some atrophy in the interossei and profound weakness below the knees. Sensation was defective peripherally for all modalities especially for position and vibration. The spinal fluid contained 3 lymphocytes and 400 mg. per cent of protein.

By August he had reached the maximum degree of disability, with good recovery of the face. Recovery of the extremities began in September and has been steadily progressive to the present. He has fairly good use of his upper extremities. He can write, but his hands are too clumsy to button his clothes and perform other fine movements. He can walk slowly with a cane but there is moderate weakness, more below the knees than above. Vibration is present but defective in the feet. Position sense is still impaired in the toes and there is some defect for cotton touch in the hands and feet.

Electrical examination was carried out on April 28, 1952. Both tibialis anticus muscles showed a chronaxie of 20 milliseconds with a tetanus ratio over 4. At rest there was fibrillary activity, and in voluntary contraction there were good action potentials of 1500 microvolts. The left orbicularis oris showed a chronaxie of 40 milliseconds and a tetanus ratio of 1.7. This indicated the presence of some normal and some denervated muscle fibers. On June 5, 1952 the right tibialis anticus and gastrocnemius were again examined and showed even more evidence of denervation. Fibrillation potentials were present at rest but were more marked in the anterior tibial. At rest also there were occasional rhythmic spontaneous motor unit potentials in the right anterior tibial muscle but none in the right calf. On voluntary contraction only one or two motor unit potentials in several areas were recorded in the tibialis anticus. These were normal to small and slightly polyphasic. Stimulation of the peroneal and tibial nerves produced slightly greater contraction than could be produced by voluntary effort but the action potentials elicited were still of very low amplitude.

A biopsy of the right anterior tibial muscle was done on June 3, 1952 at the Mayo Clinic, reported as follows: "Hematoxylin-eosin stained sections from the right anterior tibial muscle. The majority of the fibers appear normal but approximately one-third show varying degrees of degenerative change. In many of the fibers there is simply an increase in the muscle nuclei; in a few areas there is almost complete dissolution of this sarcoplasm. The interstitial tissue is relatively normal; in places it is rather edematous. No collection of round cells is observed. There are many intramuscular nerves visible on the section, and in some there is a distinct reduction in the number of axones. Conclusion: Slight to moderate degeneration of muscle fibers secondary to denervation, hypertrophy of some of the intact fibers."

DISCUSSION

These illustrative cases show the difficulty of confining description of the Guillain-Barré syndrome to any specific type either in terms of location or course. Case 1 started as a simple spinal form, gradually developed facial paralysis, and was symptom-free in ten weeks. Case 2 began with mid-thoracic root and cord symptoms, then lower extremity signs, then mild upper and only larval facial signs. This was a slowly evolving, slowly progressive, and slowly regressive syndrome, fundamentally spinal, which ran 40 weeks and left a

minimal residue in the feet. Case 4 started with cranial nerve involvement. The onset of facial paralysis was abrupt with quick recovery. At this time there was slight lower extremity involvement. Two months later there was increased weakness in the lower extremities and then the uppers became involved. Progression occurred for four more months before the process began to subside, long after the face had recovered. Now about 18 months after onset of the illness he has partially incapacitating residues in the hands and feet. Guillain's prognostication of 1916 would never have obtained in this irregular course. Case 3 was a classically "fatal" case. The picture was that of the "spinal-mesencephalic-mental" type (actually entire brain-stem) with relentless progression, "recovery," and later an exacerbation in the twenty-second week which was essentially "fatal." The case record contains two entries by the house staff indicating that the patient had "died," once "for 4 to 5 minutes." Only the resources of a well-equipped hospital and the highest level of team work changed the picture. The respirator was waiting for days outside the patient's room readied in anticipation, so that there was no loss of time or motion when the expected respiratory paralysis set in. When even the respirator failed because of plugged bronchi, the otolaryngologist was waiting to install a tracheal cannula. When this too plugged, the anesthesiologists emplaced an ingenious tracheal catheter containing a double tube, one for washing out mucus plugs, the other for oxygen. Sulfamides and antibiotics controlled the pneumonia. Case 3 was "fatal" by 1916 or 1938 standards, but not by 1951 criteria. Prognostications are of necessity relative to availability of therapeutic devices, informed personnel, and the like.

Criteria like the original ones of Guillain and Barré can no longer be used to delineate a disease. Our experience would lead us to pursue a more cautious philosophy of prognosis. It is not always true that once recovery has set in, it will continue uninterruptedly. There are as yet too many unknowns to enable us to indicate good or bad prognoses. What appears to be a favorable course running smoothly toward recovery may suddenly relapse into a new set of symptoms which may even threaten life. The reverse is equally true. What looks like a very severe paralysis of dubious recoverability may suddenly change to the picture of quick return of function (case 3).

The difficulty regarding the Guillain-Barré syndrome resides in the persistent practice of treating a semiologic complex as a nosologic entity when it is not. To resolve discrepancies the eponymic tag has been retained, but this is only a device of nomenclature. Various paralyses associated with cytoalbuminic dissociation have been found in infectious mononucleosis,[14] brucellosis,[15] diphtheria,[10,16] antirabies inoculation,[17] infectious hepatitis,[18] epidemic encephalitis,[19] peritonsillar abscess,[20] and in other types of infectious diseases. This would indicate that the syndrome is only a symptomatic response to a basic physiopathologic process.

What the nature of the etiology and pathogenesis may be is an intriguing question. Furtado[11] in studying remittent cases discussed the question of a peripheral form of neuro-allergy, and pointed out the familiar finding that

TABLE 1

VIRAL COMPLEMENT FIXATION TESTS IN CASE 3

	5–10–51	*9–21–51*	*10–2–51*
Influenza A	negative	? 1–2	negative
Influenza B	2– 1–34 = 1–64	1– 1–32 ? 1–64	? 1–2 ? 1–A
Influenza FM.	1– 1–8	2– 1–32	negative
Western equine encephalitis	negative	2– 1–2	negative
Mump	negative	1– 1–2	negative
Lymphogranuloma venereum	negative	? 1–2	negative
Psittacosis	negative	– 1–2	negative

the syndrome is often a "second illness," coming several days after some other disease. Case 3 on whom we were able to obtain detailed studies was of this type. Like Furtado's Lisbon patients, he had had the "flu" three months before and again two weeks before the appearance of his neuromuscular disease. His viral complement fixation tests (table 1) showed a maintained response to influenza B. until the October 2 level which revealed a sudden drop. The virologist interpreted the last results as a "recent bout of influenza or a very marked anamnestic response against influenza antigen. The infection was probably due to influenza B. virus." In reporting the September 21 results the virologist had asked, "Could it be that the Guillain-Barré syndrome is an allergic response of the central nervous system to repeated infections from influenza virus in which the tissue is hyperreactive?"

More suggestive evidence along this line is seen in the blood studies (table 2). Case 3 showed a relatively high eosinophilic response except during the period in the respirator when a pneumonia altered the picture. Leukopenia and relative lymphocytosis were also present during the early period of eosinophilic response. When recovery set in, the blood picture suddenly changed toward the normal except for the 11 per cent eosinophilia. Our case 2 showed similar blood responses. The lymphocytosis has been noted by Haymaker and Kernohan.[7]

The sudden massive paralysis (case 3) in the twenty-second week bears noting. This occurred after the febrile disturbance and the "chicken-pox like" rash. The rapid recovery after this exacerbation would suggest that the pathologic process must have been predominantly edema rather than inflammatory reaction. This is in keeping with Haymaker and Kernohan's idea. They considered the process a polyradiculopathy rather than a polyradiculitis because even in their 50 fatal cases, inflammatory cells were not seen until late in the course during the repair period. The final flare-up in case 3, which lasted for two weeks with rapid recession, was more like an allergic response with edema.

That the protein reaction in the cerebrospinal fluid was local, chiefly about the affected nerves, is seen in the concentrations in successive tubes (table 3).

TABLE 2

STUDIES ON THE BLOOD IN CASE 2 AND CASE 3

Case 2. *Date, 1945–46*	*12–20*	*12–22*	*1–14*	*2–23*	*3 yrs. later*	*4 yrs. later*	*5 yrs. later*
WBC	4,900	7,350	6,350	7,650	3,100	3,100	5,550
Neut							
Non-fil							6
Fil	46	50		45	52	38	54
Lymph	44	42		52	43	58	37
Mono	5	2		1	5		1
Baso	1						
Eosinophil	4	6		2		3	2

Case 3. *Date, 1951*	*4–20*	*5–4*	*9–14*	*9–15*	*9–17*	*9–18*	*10–22*
WBC	5,500	7,800	7,150	5,380	12,100	14,550	8,500
Neut. Segs	42		42	62		61	58
Unseg.			2	14		14	1
Lymph	50		54	20		21	26
Mono				2		4	3
Baso	2		1				
Eosinophil	6		1				11
Sed. Rate	14	———— pneumonia period ————					

TABLE 3

PROTEIN CONTENT OF THE SPINAL FLUID IN SUCCESSIVE TUBES

	Date	*Tube I*		*Tube II*		*Tube III*	
		Protein	*Cells*	*Protein*	*Cells*	*Protein*	*Cells*
		(mg.%)		(mg.%)		(mg.%)	
Case 2.	12–15–45	45.0	1		1		
	1–1–46	95	1	45.3	1		
	2–23–46	60.5	1				
	2–1–49	45.6	0				
Case 3.	5–1–51	255.0	2			177.0	1
	6–5–51	270.0	4	236.0	3		
	10–12–51			127.5	1	117.0	1

Invariably the second or third tubes with fluid from higher levels contained lesser amounts of protein. This may also explain the discrepancies in total protein response in some cases when only one unspecified tube is sent to the laboratory for protein determination.

Case 4 presented electrical signs of denervation in the muscles tested which is in contrast to an original statement by Guillain and Barré[2] that "alterations of electrical reactions including both the classic reactions to faradic and galvanic stimulation and the chronaxie reactions is slight in this syndrome." There was also pathologic evidence of denervation. Electrical and microscopic changes are dependent on the severity of damage to the nerve.

SUMMARY

The accumulating literature and the cases cited would suggest that Guillain-Barré's syndrome is only a symptom-complex in the course of many diseases, chiefly viral. The reaction at the point of junction of the anterior and posterior roots causes blockage and stagnation of the cerebrospinal fluid. The increased protein is believed to be due to the increased permeability of the dilated radicular and spinal meningeal vessels.

Certainly Guillain-Barré's syndrome varies both as to course and involvement, and there is no way of projecting the future even when apparent recovery has set in. It would appear that re-exposure to the original antigen may cause a resurgence of symptoms as suspected in two of our cases. The question of previous disease as the sensitizing factor is also suggested in the various studies. The course and prognosis therefore depends on etiology.

Ultimately, the now unknown may be whittled down until the entire syndrome will be absorbed into established diseases.

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Diagnostic Value of Skin Discolorations in Neurology

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SINCE the nervous system is composed of interrelated pathways and fiber groups which result in dysfunction in nervous activities in the presence of lesions, clinical examination of this system of necessity differs from that of other systems. It is important that localization of disease processes be done as exactly as possible.

Skin discolorations are very common manifestations in various neurologic conditions. While discolorations generally have little localizing value, the presence of pigmentary changes, vasomotor phenomena, scars, hypertrichosis, or alopecia contribute a great deal toward the neurologic diagnosis.

NEUROPATHIES

It is not uncommon to form more than a tentative diagnosis of neuritis merely from observing skin changes, even prior to neurologic testing of the patient. An example of this is seen in the case of a 53 year old white man who complained of aching in both arms and forearms of several months' duration, associated with recurring paresthesia. The diagnosis and etiology were immediately suggested when his shirt was removed and a dusky, erythematous encircling furrow noted about two inches above the elbows caused by habitually wearing tight sleeve holders. Pusey also considered lichenification to be a skin reaction to chronic trauma in some persons. Long-continued pressure and friction from appliances such as crutches, corsets, and truss pads could result in chloasma.[1]

Neuritis of the lateral femoral cutaneous nerve, meralgia paresthetica, poses a difficult etiologic problem at times. The nerve pursues an intraabdominal course after derivation from lumbar roots 1 and 2, becoming extraabdominal after passing beneath the fibrous attachment of the internal abdominal oblique muscle and inferior portion of the inguinal ligament, where it comes in apposition with the fascia lata. Hence, included in the conditions to which the nerve is exposed are wearing of trusses and belts by men, and, less commonly, corsets by women. Therefore, the presence of skin discoloration caused by pressure may furnish a clue as to the etiology of meralgia paresthetica.

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Bing and Haymaker[2] refer to Puusepp as pointing out that skin pigmentation occurs at times in sciatica along the course of the perforating cutaneous nerve of the sacral plexus, also the posterior cutaneous nerve of the thigh, and lateral cutaneous nerve of the calf. Discoloration sometimes appeared as early as two weeks after the initial onset.

Intercostal neuritis or neuralgia etiology may on occasion be easily determined upon observing residual brownish pigmentation and atrophic scars along the segmental distribution of an erstwhile herpes zoster. As a rule patients will tell of having suffered an attack of "shingles," but such is not always the case. For example, a 55 year old white woman who was subject to recurring extensive neurodermatitis for years eventually gave up seeking medical help. A few weeks prior to seeing a physician, she underwent an attack of herpes zoster involving the right sixth intercostal area. Believing the attack to be a recurrence of neurodermatitis, she treated herself. Persistent intercostal neuralgia after the skin lesions healed eventually caused her to seek medical advice, but only because the pain aroused fear of breast malignancy. Diagnosis and etiology were quickly determined after noting the residual skin changes. Similar postherpetic dermal sequelae of scarring and pigmentation noted on the face may be of value in making a differential diagnosis between postherpetic neuralgia and tic douloureux.

Neuritis of the trigeminal nerve, when chronic, may be accompanied by various trophic changes such as loss of facial or scalp hair and patchy loss of hair pigmentation. Glossy skin, however, as usually seen in peripheral types of neuropathy, does not occur.

So-called glossy skin is a fairly common secondary result of neuritis described by Paget in 1864. The sites of predilection involve the extremities, especially the fingers. The affected skin is reddish or purple "like that of a chilblain," later becoming whitish or grayish, glossy, and shining, the surface to some extent resembling a polished atrophic scar. Fissuring and ulceration may occur. Atrophic changes in the appendages include loss of hair and curving of the nails, transversly and longitudinally. Neuralgic pains are present to a lesser or greater degree and distinguish causalgic cases in general.

While various local neuropathies are intimately associated with discolorations, as described above, neurofibromatosis (Von Recklinghausen's disease) is frequently characterized by skin discoloration bearing no direct relationship to neuritic involvement. Neurofibromatosis, a congenital neuroectodermal dysplasia, typically involves multiple skin tumors which are frequently associated with nerve neoplastic formation. The anomalous skin pigmentation is in the form of "coffee spots" and may be located on almost any part of the body. Pigmentation may also consist of light or dark brown freckling and precede or accompany tumor formation. Nevi may co-exist with the "giant freckles." The pigmentary changes help to rule out lipomatosis and adiposis dolorosa (Dercum's disease). The latter is a vasomotor-trophic disease in which pain is especially prominent in areas of nodular formation, apparently due to invasion of the sensory nerve endings by fat tissue.

Polyneuritis may be a complication developing in almost any toxic and metabolic disease. However, in certain instances the presence of more or less characteristic pigmentary changes quickly suggests the clinical and laboratory approach in arriving at a basic diagnosis. For example, a "lead line" noted about the tips of the gum papillae immediately suggests plumbism as the probable cause of an existing polyneuritic syndrome.

A diffuse skin discoloration is noted in pellagra. Here erythematous patches are seen early, resembling simple sunburn and affecting the dorsum of the hands, cheeks, nose, and exposed parts of the neck and upper chest. There may also be an involvement of the ankles, genitals, and perineum. One usually sees a dull red erythema, occasionally edema, then scaling, and finally a gray-brown hyperpigmentation of the involved areas. The dermatitis and pigmentation are sharply demarcated from the palms and palmar surfaces of the fingers, extending to both wrists and partially up the forearms to form a so-called "pellagrous glove."[3] Polyneuritis associated with pellagra are described by Hein and Merrill[4] as alterations limited to the legs, consisting of sensations such as burning, tingling, and aching, with occasional attacks of sharp pain.

There may be a close resemblance to acute porphyrin intoxication in the polyneuritic and other clinical features of pellagra.[5] However, there is a distinction in the proverbial three "d's" of pellagra (diarrhea, dementia, dermatitis), in that the skin pigmentation noted in porphyrinuria lacks the inflammatory characteristics of pellagra. According to Sutton and Sutton,[1] hematoporphyria results from breaking down of the hemoglobin molecule, causing hematoporphyrin to act as a photodynamic sensitizer rendering tissues more susceptible to ultraviolet rays. Consequently, pronounced "tanning" of exposed areas results. Porphyrinuria is characterized by a urine which is sometimes port-wine color and at other times brown or blackish, especially after exposure to sunlight.

SPINAL CORD DISEASE

In certain spinal cord syndromes, pigmentary changes of the skin may occur which frequently may be almost pathognomonic. Some of these changes may be more or less general in distribution or confined to the extremities receiving segmental distribution from diseased areas of the spinal cord. In other instances, localized trunk discolorations may suggest the etiology of a disease process.

For example, sensory changes in the extremities described as a feeling of numbness or tingling may constitute some of the earliest subjective manifestations of pernicious anemia, and may be prodromal to subacute combined degeneration of the spinal cord. The first point to attract the examiner's attention is a lemon-yellow facial color and pallor of the lips. This lemon tint is quite characteristic and suggests the diagnosis at once. In some cases a simple pallor is seen, and, less commonly, obvious jaundice.[6] Petechiae may occasionally appear over the body.

Segmental dermal changes are revealed in syringomyelia, which may present pathognomonic sensory changes consisting of ability to perceive touch but absence of pain and temperature modalities in parts of the extremities or trunk. There may be no other symptoms than this sensory dissociation, and attention may be drawn to it first upon development of skin lesions in the analgesic part owing to the effect of burns, cuts, or other injuries. It may also give rise to lesions such as paronychia, ulcers, or local necrosis and gangrene (Morvan's disease). According to Grinker,[7] vasomotor changes in the latter, which is a form of syringomyelia, resemble Raynaud's disease to some extent. In addition, the back of the hand is cold, glossy, livid, and edematous (Marinesco's so-called "main succulente"). Soft tissues of the hand may proliferate (chiromegaly); there may be abnormal skin dryness, scaling, fissuring ("toad skin"), and a tendency to develop herpetic eruptions.

Not infrequently, valuable information will be suggested by the coexistence of congenital metameric skin abnormalities and certain spinal cord syndromes. Wechsler[8] has pointed out that the presence of a tuft of hair over the sacral region, frequently on a pigmented depression, should arouse suspicion of the existence of spina bifida occulta. While it is true that the localizing value of such manifestations is very limited, pigmentary changes and hypertrichosis may occur over the vertebral abnormality.[9]

Bailey[10] has reported that multiple telangiectasis in the skin and mucous membrane have been associated with similar lesions in the central nervous system. Much diagnostic emphasis has been placed by various authors[11] on the presence of a skin nevus in the dermatome corresponding to an approximate level of the spinal cord where signs and symptoms of a cord tumor exist. Surgical exploration frequently reveals the fact that the neoplasm is a hemangioma.

INTRACRANIAL DISEASE

Telangiectasis and nevi are suggestive when found on the neck, face, or scalp in a case presenting clinical evidence of an intracranial neoplasm. However, these lesions are of no practical localizing value insofar as a suspected angioma is concerned. On the other hand, nevi vasculosi present in the distribution of one or more branches of the trigeminal nerve, as characterized in Sturge's disease, is associated with neurologic symptoms permitting comparatively accurate intracranial localization. These symptoms include Jacksonian epilepsy and hemiplegia and body hemiatrophy on the side opposite the facial nevi. Intracranial pathology usually consists of cerebral calcification ipsilateral to the skin nevi and angiomatous changes of the pial vessels. Vascular changes may also be found in the ocular fundus homolateral to the nevi.

Certain skin discolorations which may be practically pathognomonic appear as a result of intracranial infection. For instance Hoyne[12] pointed out that the existence of petechiae in a case of meningitis is almost sufficient evidence for considering meningococci as the cause of the infection, and that it is only with the greatest rarity that petechiae appear in any other form of meningitis.

The lesions, if not found on the skin, may be seen in the conjunctiva after the lower eyelids are turned down.

Petechiae which appear in cerebrospinal meningitis do so prior to meningeal involvement, during the stage of invasion of the blood stream. Brinton[13] described pigmentation as appearing at any time during the first eight days, but usually present by the first or second day. The rash reaches full development in a few hours, remains unaltered for a day or two, then fades, leaving a brownish discoloration which disappears on or about the fourth day of the infection. The rash, which varies in size and color, is usually small, rose-red or brick, and two to three millimeters in diameter. The lesions in general "resemble those remaining after all acute reaction has subsided from a flea-bite." Bing and Haymaker described a special form of dermographism occurring in the infection due to increased vasomotor irritability, termed "tache cerebrale;" that is, touching the skin causes a flaming red spot to appear which persists for a considerable period of time.

Crafts,[14] in his monograph, drew attention to a wide variety of skin conditions in the numerous manifestations of epidemic encephalitis which he felt had been overlooked or considered not to be an essential part of the disease. He believed that different forms of eruptions occur with sufficient frequency to consider them as important. These include eruptions presenting a fine macular appearance that resemble an acute exanthem, located on the chest, neck, or side of the face, as a patchy flush evidently based on vasomotor changes similar to the general deep-livid or salmon-pink flush seen in late cases and parkinsonism. At times a chloasmic-like pigmentation may occur which is general in distribution or localized to the face and neck, presumably due to adrenal gland dysfunction. Acne-like eruptions on the back or occurring more extensively are described which may be so pronounced as to resemble light smallpox or chickenpox. These leave dusky red points which are slow to fade. The eruptive state may also include small vesicles or frank herpetic crops resembling zoster or labial types. Minute petechiae have been seen in rare cases.

The presence or a history of jaundice is diagnostically important in a clinical history associated with neurologic findings suggesting involvement of the extrapyramidal motor system, such as occurs in progressive hepatolenticular degeneration. Wilson[15] stated that the onset of symptoms in adolescence and early adult life consisting of tremors, bilateral athetoid movements of the extremities and of the face, markedly increased muscle tonus, and emotional disturbance should be considered as progressive lenticular degeneration, especially if there was evidence of liver malfunction at any time. He added that a pigmented corneal ring confirms the diagnosis.

The eye is not related to the skin, of course, but since the essential purpose of this review is to describe easily observed body discolorations, perhaps there is justification for including corneal discoloration. The pigmented corneal ring is an inconstant but characteristic feature of progressive hepatolenticular degeneration. The ring consists of greenish-yellow or greenish-brown pigment

on the under-surface of the cornea near its limbus in Descemet's membrane. The grains are fine and closely set towards the periphery, forming a band or color zone which obscures the subjacent iris but may become more scarce and discrete towards the center. It is difficult to see in brown eyes, and can exist before neurologic symptoms develop. Brain[16] also found the ring present with sufficient frequency to render it of diagnostic value.

While frequently accompanied by a demonstrable basophilic adenoma of the anterior lobe, the basophilic syndrome of Cushing has not yet been assigned a definite status. Regardless of whether the pathologic changes are primarily in the pituitary, adrenal, or thymus, or secondarily in the two organs named last, definite aid toward diagnosing Cushing's syndrome is offered by the skin changes. Soffer[17] described striae atrophica as a consistent phenomenon usually present over the lower abdomen, flanks, buttocks, upper part of the thighs and arms, and often extending along the outer aspect of the breasts. They are usually parallel and violet in color. Such striae may be observed in ordinarily obese individuals, but differ in that there is absence of color. The skin may become generally mottled like that observed in cutis marmorata, but usually is limited to the extremities and less frequently to the face. Skin changes may also include a diffuse dusky hue and cyanotic coloring of the lips and nailbeds.

General pigmentation in hypophyseal cachexia (Simmond's disease) may offer diagnostic assistance. While this disease is frequently confused with anorexia nervosa, evidence that 24 per cent of cases of the former[18] reveal some degree of pigmentation varying from yellow to brown should prove helpful in differential diagnosis. Although Berkman[19] found that approximately 13 per cent of cases of anorexia nervosa reveal skin discoloration, these changes consist of brownish pigmentation involving the abdominal skin.

Simmond's disease may have to be differentiated from Addison's disease on occasion because a patient afflicted with the latter can be considerably underweight. However, the characteristic bronze pigmentation of adrenal cortical insufficiency is usually unmistakable, as is typical pigmentary spotting of the mucous membrane.

Tuberous sclerosis is a congenital neuro-ectodermal dysplasia characterized by retarded mental development, epileptic seizures, and sebaceous adenomas. The intracranial lesions of tuberous sclerosis resemble glial tumors, but congenital multiple sebaceous adenomas make the diagnosis possible during life.

AUTONOMIC DISORDERS

Disorders of the autonomic nervous system present the largest group of syndromes wherein skin discoloration is of paramount importance for neurologic diagnosis. While pain symptoms are frequently outstanding complaints in the vasomotor and trophic disorders, it would be difficult indeed to make a diagnosis without the appearance of some kind of color change. Kraus[20] stated that probably all of these diseases depend on some unknown disturbance in the sympathetic system "between its origin in the subthalamic region

of the central nervous system and its endings in the different structures." On the other hand, clinical experience reveals a definite predisposition to psychopathology in many persons subject to vasomotor and trophic disturbances.

Harris[21] described dermographism as an important and practical vasomotor reaction in certain neurologic lesions. When a pointed instrument is drawn heavily across the skin, there are normally, first, reddening of the area; secondly, spreading of the flush ("flare"); and, thirdly, development of a wheal. The flare is more pronounced and of longer duration in the presence of a recent sympathetic lesion. If a peripheral nerve is severed, an exaggerated flare may be induced in the corresponding area up to six days after the injury. There is no flare thereafter. However, if there is an anesthesia of the part but the flare can still be produced after the sixth day, the lesion must lie in the cord or brain unless the anesthesia is hysterical in origin.

Angioneurotic edema (Quincke's edema) has no practical application comparable to dermographism. It consists essentially of attacks of cutaneous swelling, usually multiple, the lesion being pale or slightly reddish, varying in size from about one to three or four inches in diameter. The affected skin has a doughy consistency and pits when pressure is applied. Swelling may appear anywhere on the body and frequently affects the viscera. Kennedy[22] has described cases in which transient cerebral symptoms were noted at the time of eruption, consisting of hemiplegia, headaches, and local twitchings. He assumed that circumscribed edema could also appear on the leptomeninges and produce cerebral symptoms.

Acrodynia, which has various synonyms such as Swift's disease, "pink disease," and erythredema polyneuritis, is often considered to be a disorder of the autonomic nervous system. It affects infants chiefly and portends a grave prognosis. A change in the patient's disposition, extreme general discomfort, and suffering are characteristic. Butler emphasized changes in the hands and feet which he considered almost pathognomonic: redness, swelling, itching, and pain. Bilderbach and Cobb called attention to the five "p's:" pinkness, peeling, paresthesia, perspiration, and photophobia.

Weir Mitchell was the first to describe erythromelalgia as a vasomotor neurosis. The condition appears exclusively in adolescents, especially males. Vasodilatation is typically observed in the extremities, more so in the legs. In one form it may involve the peripheral parts of the extremities in a diffuse and symmetrical pattern, while in another there may be distribution to a region innervated by certain nerves and associated with signs of atypical neuritis. The first sign of an attack is neuralgiform pain followed by intense redness of the toes, feet, and sometimes part of the calf, but rarely an entire extremity. The area of reddening, which is due to vasodilatation and usually accompanied by swelling, is sharply demarcated. Pain becomes more severe as vasodilatation increases. It may be necessary to rule out erysipelas. Bing and Haymaker also mentioned erythromelia as requiring a differential diagnosis. In this disorder, however, vasodilatation is painless and affects only extensor surfaces of the extremities.

Bing[23] was the first to describe facial erythromelalgia, which he termed "erythroprosopalgia." This condition begins suddenly with a burning pain and reddening of the skin around the eyes and cheeks in an "automobile goggles" distribution.

While most vasomotor disorders are rare, acroparesthesia is relatively common. It occurs predominantly in women between the ages of 40 to 55 years, and psychopathologically-predisposed individuals are more susceptible. The syndrome is characterized by attacks of paresthesia such as formication, prickling, tingling, stinging, and sometimes pain. There is an initial pallor and cyanosis of the hands and feet, followed by an intense livid discoloration which is usually bilateral. Reddening of the fingers and toes may be an aftermath of the attack. Raynaud's disease will occasionally have to be ruled out.

Raynaud's disease occurs most frequently in 25 to 30 year old women, and is also characterized by a tendency to local vasomotor skin changes. That is, one or more fingers or toes, border of the ears, or tip of the nose may suddenly become white and cold. Paresthesias are outstanding. Local asphyxia can occur with production of variegated shades of color, which may be diffuse or speckled, ranging from a blue-gray cyanotic hue to blackness caused by gangrene. Vesicles form at times, filled with a serous, bloody, or blue-black fluid.

The relationship of Raynaud's disease to scleroderma has been brought out by many observers due to some similarity in trophic changes, and because vasomotor disturbances may precede or accompany skin induration common to both diseases. Scleroderma, however, is a skin disease and a disorder of the autonomic nervous system, characterized principally by thickening, atrophy, and pigmentary changes. The lesions present yellow or brown pigment which may be interspersed with vitiliginous patches. A lilac ring often surrounds an area of scleroderma. In cases where vasomotor disturbances are prominent, distinction from Raynaud's disease becomes difficult indeed. However, a mask-like facies[24] similar to that noted in parkinsonism and additional evidence of scleroderma elsewhere assists in distinguishing between the two syndromes.

While scleroderma may be associated with facial hemiatrophy,[25] the atrophy can constitute a vegetative neurotrophic disorder.

Progressive facial hemiatrophy occurs chiefly in young women and is insidiously progressive. In view of the likelihood that both sides of the face are rarely, if ever, entirely symmetrical, it may be that asymmetry denotes a pathologic process when associated with patches of facial vitiligo, abnormal pigmentation, patchy graying of the hair, and ipsilateral loss of scalp hair. The patient's chief complaint is usually neuralgiform pain over the affected side.

Progressive facial hypertrophy is a counterpart of hemiatrophy, characterized in some cases by vasomotor disturbances and similar pigmentary changes. According to Bing and Haymaker, this disorder, in contrast to atrophy, most often affects the right side of the face.

Chronic progressive hypertrophic acrocyanosis is a vasomotor-trophic dis-

order wherein soft parts of the hands and feet hypertrophy. It must not be confused with acromegaly. The involved areas become cyanotic or intensely red. A slow, progressive course differentiates it from Raynaud's disease, and lack of pain from erythromelalgia.

An interesting vasomotor reaction occurs in the auriculotemporal syndrome (Frey's syndrome), resulting from destructive lesions of a parotid gland. The lesion tends to set up a complicated reflex act in response to taste stimulation of the posterior part of the tongue, and includes the glossopharyngeal, small petrosal, auriculotemporal, and facial nerves,[26] and vasomotor secretory vegetative fibers. The reaction consists of a combination of flushing on the cheek and pinna, with profuse sweating over an area which corresponds to the auriculotemporal branch distribution. While a "pretending to eat" type of motor activity can cause slight redness to appear, it is usually necessary to ingest an acid kind of substance such as apple or a solution of vinegar to bring out the complete vasomotor effect.

MISCELLANEOUS

There are some neurologic manifestations resulting from or associated with several disease entities which, for the purpose of this review, could best be classified as a miscellaneous group.

Neurologic complications from hemorrhagic diseases, while relatively rare, are due to hemorrhage within or around nervous tissue.[27] If intracranial bleeding occurs, symptoms can begin abruptly with collapse, coma, and death, or gradually over a period of several or more days. Focal phenomena may result, such as pareses and hemiplegias, aphasias, sensory changes, visual field defects, reflex abnormalities, and various mental symptoms. The cause of the neurologic symptoms is quickly suggested by skin hemorrhages, varying from petechiae to massive ecchymoses.

A similar involvement of the nervous system may take place in polycythemia. Skin changes include a generalized bluish-red cyanosis, particularly noticeable in the lips, ears, and finger tips.

Silverstein[28] described petechiae as diagnostic and even pathognomonic of cerebral fat embolism. Following trauma, petechial lesions usually appear on the third day, but may become apparent within the first 24 hours, and are seen over the upper part of the chest, shoulders, mucous membranes, and at times only in the conjunctivae. Almost any type of physical injury can result in cerebral fat embolism. The clinical features include a lucid interval followed by sudden development of rapid pulse, pyrexia, and dyspnea, and various neurologic symptoms indicating diffuse and extensive involvement, especially that of decerebrate rigidity. Lipuria, which may be determined by a simple test,[29] corroborates the diagnosis.

Some forms of muscular dystrophy are associated with pigmentary changes which may be helpful in the diagnosis. For instance, in the pseudohypertrophic type, linear changes resembling the stria of pregnancy may occasionally be seen covering an involved muscle.

While myotonia and muscular wasting are characteristic of dystrophia myotonica these changes may develop independent of one another, and in the absence of atrophy it can be confused with myotonia congenita (Thomsen's disease). The myotonus in Thomsen's disease greatly overshadows any muscular disability, whereas the reverse is true in dystrophia myotonica. However, in 1918 Fleischer demonstrated that cataract formation occurs in the latter and when present at any early age may be the only expression of the disease. The cataracts may appear through a series of generations before onset of myotonia or muscular dystrophy. Cataracts do not appear in Thomsen's disease.

The cataract is characterized[30] by punctate and linear multicolored opacities in the anterior and posterior subscapular zones. It may develop to a degree where cataracts can be seen with the unaided eye or, perhaps, with use of a flashlight.

Stigmata of congenital syphilis should be known in order to recognize the syphilitic etiology of later-appearing nervous symptoms. These stigmata include "Hutchinson's teeth," rhagades, and cutaneous scars over the body resulting from healing of various cutaneous luetic lesions.

There are other disease entities which may present neuropathologic symptomatology and are associated with skin discolorations. These include rashes characteristic of the rickettsial group, exanthems, purpuras and ecchymoses of chemical poisonings, drug reactions, and cyanosis or jaundice due to systemic involvement. However, most of the syndromes incorporated in this review are those which will best demonstrate a relationship between discolorations and the diagnosis of neurologic disease.

SUMMARY

This is a review intended to point out the diagnostic importance of skin discolorations which may exist with neurologic symptomatology. The neurologic syndromes are discussed in groups referable to neuropathies, the spinal cord, encephalopathies, the vegetative nervous system, and a miscellaneous group of diseases which also bear a direct relationship to skin discolorations, neurologic symptoms, and diagnosis of the basic disease entity.

The relations between skin discolorations and neurologic disease may be classified to some extent as follows: 1) direct relationship between discoloration and neurologic disease, for example, herpes zoster; 2) discoloration as a facet of a hereditary or congenital neuropathologic process, for example, "café au lait" spots in Von Recklinghausen's disease and nevi associated with hemangiomas; 3) discoloration as an intrinsic component in a neurologic syndrome, for example, vasomotor changes of the skin in disorders of the autonomic nervous system; 4) discoloration as a primary manifestation in diseases which secondarily involve the central nervous system, for example, hemorrhagic disease; 5) discoloration as a secondary manifestation in diseases which primarily involve the central nervous system, for example, "rose-spots" of cerebrospinal meningitis.

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Hypoglycorrhachia of Non-Infectious Origin: Diffuse Meningeal Neoplasia

Leonard Berg, M.D.

HYPOGLYCORRHACHIA, or an abnormally low cerebrospinal fluid sugar content occurring in response to diffuse neoplastic involvement of the leptomeninges, was recorded as early as 1904.[1] Although other such instances have been reported since then, the relationship has not received sufficient emphasis. In particular, the diagnostic importance of this phenomenon has been stressed in only two publications, one in the French literature[2] and one recent American paper.[3] The purposes of this presentation are: 1) to establish this association as an important clinical syndrome occurring in a wide range of meningeal neoplastic diseases, and 2) to report five additional cases.

Non-neoplastic, yet non-infectious, causes of hypoglycorrhachia may be dispensed with briefly at the start. Dependence of the glucose level in the cerebrospinal fluid upon that in the blood is well known. Reduced spinal fluid sugar content as a result of hypoglycemia is then to be expected and has been documented.[4]

That the chronic meningitis of Boeck's sarcoid may be accompanied by hypoglycorrhachia is now proved by reports of four autopsied cases[5–7] as well as several clinical reports.[8–10] (True, Boeck's sarcoid may be yet demonstrated to be of infectious etiology, but it is not usually grouped with the infectious diseases.)

Lowered spinal fluid sugar values have also been reported rarely in subarachnoid hemorrhage.[11,12] The sugar content tends to return rapidly toward normal. The abnormal values have variously been attributed to glycolytic action of the blood and to obstruction of the choroid plexus by clots, but proof is lacking.

CARCINOMATOSIS

Scholz[13] in 1905 and Heinemann[14] in 1911 reported cases of meningeal carcinomatosis in which the spinal fluid did not reduce Fehling's solution. Since the introduction of quantitative techniques for cerebrospinal fluid sugar

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determinations, 13 additional cases* of this disease with a sugar content less than 40 mg. per cent have been published.** In six of these the value was 20 mg. per cent or below. Possibly abnormal levels of 44, 46, and 48 mg. per cent have been reported in three additional cases[15–17] whose blood sugar determinations were not given. An unequivocally normal cerebrospinal fluid sugar content (82 mg. per cent) has been recorded only once in the literature[18] in association with diffuse carcinomatous invasion of the meninges.

GLIOMATOSIS

Spinal fluid sugar content has been recorded in the literature for six cases of diffuse gliomatosis of the meninges. The cases of Rindfleisch[1] and Batten[19] were described as "diffuse sarcomatosis" but were almost certainly instances of diffuse medulloblastoma arising from primary sites in the roof of the fourth ventricle. Bailey and Cushing[20] considered them as such. The cerebrospinal fluid in each case did not reduce Fehling's solution. This was also true in an instance of disseminated glioblastomatosis[21] and in a case of diffuse glioma, probably an astrocytoma.[22] On the other hand, the diffuse leptomeningeal glioblastoma reported by Marcuse[23] was accompanied by spinal fluid sugar contents of 50 and 68 mg. per cent. A recently reported case[24] of diffuse astrocytoma had a single cerebrospinal sugar determination of 65 mg. per cent six months before death. It is possible that a later lumbar puncture may have revealed some abnormality.

Briefly, then, hypoglycorrhachia has been recorded as a result of the following diffuse gliomas: medulloblastoma (two cases), glioblastoma (one case), astrocytoma (one case). A normal cerebrospinal sugar content has been observed once in diffuse glioblastoma and once in diffuse astrocytoma.

CASE REPORTS

Three cases of diffuse gliomatosis of the meninges, two of which had a low sugar content in the cerebrospinal fluid, have been studied at the Neurological Institute of the Presbyterian Hospital in New York.

Case 1.—A 43 year old mechanic was transferred to the Neurological Institute of New York on October 6, 1952 from another hospital. His illness had had its onset one year previously with numbness and progressive weakness of both lower extremities. Two months later difficulty with urination had appeared and progressed slowly to complete urinary retention. For three months he had been unable to walk because of paraparesis. Intermittent headaches, occasional stiffness of the neck, and vomiting had appeared in the last two or three months.

On admission the patient was alert and cooperative. Except for evidence of moderate weight loss, the general physical examination was not remarkable. On neurologic examination there was a complete flaccid paralysis of the lower extremities and abdominal musculature. There was severe diffuse muscular atrophy in both lower extremities and mild incoordination of fine movements of both upper extremities. Tendon reflexes were hypo-

*Individual references have been cited in table 4.

**Dr. Lillian Strange of this institution presented a paper on meningeal carcinomatosis before the 1952 meeting of the American Neurological Association. These cases were briefly summarized in the Association's Transactions (1952, p. 181) and will be the subject of a future publication. Of seven cases with cerebrospinal fluid sugar determinations, six had levels below 40 mg. per cent.

TABLE 1

CEREBROSPINAL FLUID STUDIES — CASE 1

Date	*Site*	*Cells*	*Protein*	*Sugar*	*Chloride*
1952		cu. mm.	mg. per cent	mg. per cent	mg. per cent
7/2	Lumbar	5	250	14	695
7/11	"	7	140	25	—
8/2	"	0	1,000	10	—
8/19	"	0	1,275	10	660
9/10	"	0	1,800	15	690
10/8	"	3	3,700	37	641
10/9	Cisternal	3	576	28	666

active in the upper extremities and hyperactive in the lower extremities except for an absent right patellar reflex. Bilateral extensor toe responses were present. Pain, touch, and temperature sensibilities were absent below the sixth thoracic dermatome. Vibration and position senses were absent in the lower extremities. Examination of the cranial nerves was entirely normal except for blurring of the right optic disk margins. There was slight nuchal rigidity and photophobia.

Laboratory data included a fasting blood sugar of 85 mg. per cent. Cerebrospinal fluid studies elsewhere and at this hospital are recorded in table 1. Wassermann reaction and multiple cultures were negative.

The patient's course was consistently afebrile. On October 9 lumbar and cisternal myelography was performed. The contrast medium flowed slowly and tended to loculate throughout the spinal subarachnoid space. Complete block was met at the eighth thoracic intervertebral space from both lumbar and cisternal instillations.

On October 12 mental aberrations consisting of mild confusion, restlessness, and visual hallucinations were noted for the first time. These abnormalities tended to increase.

A thoracic laminectomy was performed on October 21. The leptomeninges were thickened and opaque. A reddish, friable, and very vascular mass was found adherent to the cord at the level of the myelographic block. Attempts to remove the mass were unsuccessful.

Three days later the patient, who had been doing well, suddenly became comatose and died in two hours. The clinical diagnosis was cryptococcosis of the central nervous system.

At autopsy there were no significant gross abnormalities of the brain. The leptomeninges of the cord, however, were strikingly abnormal. A diffuse irregular opacity of the leptomeninges obscured the underlying cord from the midcervical cord down to the sacral segments (figure 1). There were in addition a number of nodular protuberant opaque masses in the leptomeninges, the largest of which was present at the level of the ninth thoracic cord segment. On transverse section the middle and lower thoracic cord was infiltrated by finely granular tissue confluent with that in the meninges. Microscopically the abnormal tissue in the leptomeninges was a highly cellular neoplasm composed chiefly of rather small cells with scanty cytoplasm and oval nuclei (figure 2). Larger cells, some multinucleated, and some elongated bipolar cells were also seen. Mitoses were frequent. Occasional small zones of hemorrhage and necrosis were found, the latter resulting in pseudopalisades. Phosphotungstic acid stain revealed blue staining fibers among the tumor cells. The histologic appearance was characteristic of glioblastoma.

The leptomeninges were heavily infiltrated over the entire cord and to a lesser extent over the brain stem, hypothalamus, cerebellum, and many areas of cerebral cortex. Superficial invasion of the parenchyma was common, but massive invasion had occurred only in the lower thoracic cord (figure 3). In all areas leptomeningeal tumor seemed primary and parenchymal invasion secondary.

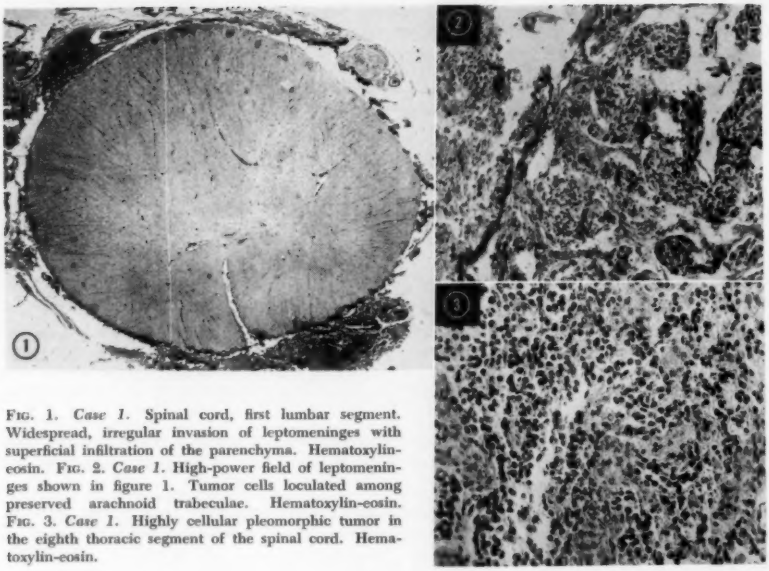


FIG. 1. *Case 1.* Spinal cord, first lumbar segment. Widespread, irregular invasion of leptomeninges with superficial infiltration of the parenchyma. Hematoxylin-eosin. FIG. 2. *Case 1.* High-power field of leptomeninges shown in figure 1. Tumor cells loculated among preserved arachnoid trabeculae. Hematoxylin-eosin. FIG. 3. *Case 1.* Highly cellular pleomorphic tumor in the eighth thoracic segment of the spinal cord. Hematoxylin-eosin.

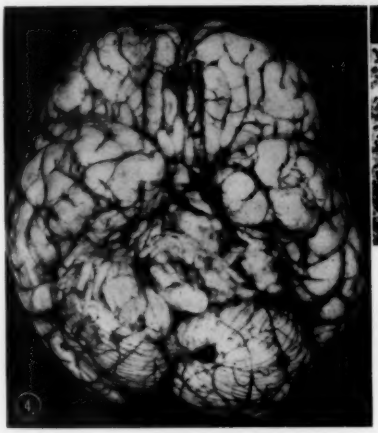
That hypoglycorrhachia is not a uniform finding in cases of diffuse glioblastomatosis is emphasized by the following case:

Case 2.—A 43 year old housewife was admitted to the Neurological Institute on April 7, 1945. Eleven weeks prior to that date she had first experienced girdle pains in the subscapular areas, radiating anteriorly. Seven weeks before entry weakness of both lower extremities had appeared and progressed rapidly to complete paraplegia. Later there had been numbness below the chest, loss of sphincter control, headaches, and stiff neck. On examination there was a low grade fever, nuchal rigidity, paraplegia with hyperreflexia and bilateral extensor plantar responses, almost total loss of sensation below the fourth thoracic dermatome, and bilateral papilledema.

The fasting blood sugar was 106 mg. per cent. The spinal fluid was under a pressure of 400 mm. of water. The fluid was xanthochromic and contained 8,000 red blood cells, 10 leukocytes, 5,000 mg. per cent protein, and 78 mg. per cent sugar. A ventriculogram performed on April 11 was interpreted as suggesting multiple cerebral tumors, but biopsy attempts at craniotomy were unsuccessful. The patient expired at the close of the procedure.

The result of postmortem study was the finding of glioblastomatosis of the leptomeninges, with the most severe involvement over the medial surfaces of the frontal lobes and over the thoracic cord. Gross tumor masses were present in both these locations and to a lesser degree in the entire subarachnoid space from the midcervical cord to cauda equina. On microscopic examination there were clumps of cells in the leptomeninges about the brain stem as well. In all tumor sites the leptomeninges were distended and appeared to be the primary site of neoplasia, superficial parenchymal invasion seeming to be secondary.

Comment: Both these glioblastomas were considered to have arisen primarily in the leptomeninges and to have invaded the parenchyma only secon-



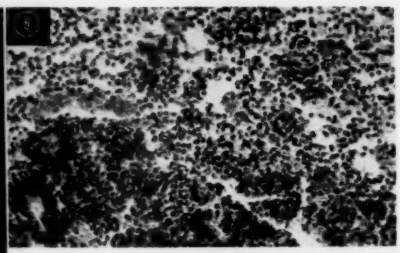


FIG. 4. *Case 3.* Base of the brain. Tumor distending the left cerebellar hemisphere, distorting the brain stem, and spreading widely in the subarachnoid cisterns. FIG. 5. *Case 3.* High-power view of tumor in cisterna interpeduncularis illustrating its characteristic features. Hematoxylin-eosin.

darily. Thus, they probably fall within the group of primary extramedullary gliomas recently emphasized by Cooper and his coworkers[25] and thought to arise from heterotopic meningeal glial rests.[26]

A third diffuse malignant glial tumor was accompanied by hypoglycorrhachia:

Case 3.—A 21 month old male infant was admitted to the hospital on July 19, 1938. He had been ill for one week with headache, vomiting, unsteady gait, and weakness of the right side of the body. On examination the gait was wide-based. There was a right hemiparesis and pyramidal tract signs were present in the right extremities. On July 30 and 31 the cerebrospinal fluid was under pressure of 200 mm. of water. The fluid was slightly opalescent and contained 80 mg. per cent protein, and 16 and 28 mg. per cent sugar. There were 300 to 400 cells per cu. mm. About one-half were lymphocytes or polymorphonuclear leukocytes. The remainder, as seen in a wet preparation stained with methylene blue, were described as large, irregular cells arranged in clumps. Their nuclei were large and round with irregular masses of chromatin. These cells were considered to be "medulloblasts." The blood sugar was not recorded.

In early August the child became drowsy and apathetic. Ptosis of the left lid, mydriasis, paralysis of the left external rectus muscle, and pallor of the optic disks were noted. On August 11 ventriculography was performed. There was symmetrical dilatation of the lateral and third ventricles but the aqueduct and fourth ventricle were not visualized. These findings were considered to be consistent with a diagnosis of a cerebellar tumor. This, plus the report of probable tumor cells in the cerebrospinal fluid, indicated that there was an inoperable posterior fossa neoplasm. No further operative procedures were carried out. The patient became comatose, manifested respiratory difficulties, and died on August 14, 1938.

At autopsy there was a large, friable tumor mass (figure 4) invading and destroying the left cerebellar hemisphere, left half of the pons, upper medulla, and most of the midbrain. It grew into the subarachnoid space of the left cerebellopontine angle, around the medulla, and also into the leptomeninges of the interpeduncular fossa, hypothalamus, and left hippocampal fissure. Histologically, the tumor cells were closely packed, showing scanty cytoplasm and oval nuclei, some with a fine chromatin network and others hyperchromatic.

For the most part, the cells were arranged in coalescent columns which formed a coarse meshwork (figure 5). True rosette formation and mitoses were frequent. No blue-staining fibrils were revealed by Mallory's phosphotungstic acid stain. Unfortunately autopsy permission was limited and the spinal meninges could not be examined.

The final diagnosis was "medulloepithelioma of the brain stem and cerebellum with invasion of the leptomeninges." This malignant tumor was certainly of glial origin and probably is best classified in the ependymoma group, perhaps as an "ependymoblastoma." According to Kernohan's recent classification,[27] it would be an ependymoma, grade three or four.

SARCOMATOSIS

This phase of the subject is difficult to review because of the lack of general agreement as to diagnostic pathologic criteria. Well defined subgroups, such as the melanosarcomas and the lymphoma group, will be considered later.

Hypoglycorrhachia was observed by Bronfman and Reumont[2] in their cases 2 and 3. The former was accepted by Black and Kernohan[28] as an instance of primary diffuse tumor of the meningeal connective tissue. Their case 3, according to the authors, was accepted by Bailey as a primary sarcoma of the brain with diffuse leptomeningeal spread. Their case 1, also accompanied by hypoglycorrhachia, is not included here because of lack of postmortem examination.

Another instance of what appears to be a primary diffuse leptomeningeal tumor, reported by Marburg and his coworkers,[29] was accompanied by a cerebrospinal fluid sugar as low as 30 mg. per cent. Two other cases[30,31] accepted by Black and Kernohan as primary diffuse meningeal neoplasias had normal cerebrospinal fluid sugar levels.

Thus, three of five cases in this group were accompanied by hypoglycorrhachia.

LYMPHOMA-LEUKEMIA

Diffuse leptomeningeal infiltration is one of the rare neurologic complications of this group of diseases, extradural mass formation being far more common. Cerebrospinal fluid sugar determinations on four patients with diffuse leptomeningeal spread of lymphoma or leukemia are recorded in the literature. The case of Critchley and Greenfield[32] (myelocytic leukemia) had a cerebrospinal fluid sugar level of 19 mg. per cent. The value was as low as 33 mg. per cent in the patient reported by Schwab and Weiss[33] (acute lymphatic leukemia). However, a patient with leptomeningeal spread of a Hodgkin's granuloma[34] and one with an unclassified malignant lymphoma[35] both had a normal sugar content.

Two proved cases of diffuse lymphomatous invasion of the leptomeninges have been studied at the Neurological Institute. Hypoglycorrhachia was evident in both.

Case 4.—A 3 year old boy was admitted to this hospital on May 16, 1936 with an illness of six weeks' duration characterized by intermittent headache and vomiting. He was acutely ill and drowsy. There was moderate weight loss and an effusion in the left pleural cavity. There was generalized weakness and ataxia but no focal neurologic abnormalities. Later proptosis of the left eye, bilateral external rectus palsies, and left facial

TABLE 2

CEREBROSPINAL FLUID STUDIES — CASE 4

Date	*Cells*	*Lymphocytes*	*Protein*	*Sugar*	*Chloride*
1936	cu. mm.	per cent	mg. per cent	mg. per cent	mg. per cent
5/17	6,500	95	125	42	760
5/18	5,600	97	107	46	730
5/21	2,500	—	330	35	720
5/25	3,500	—	—	38	750
5/27	2,200	100	320	27	680

weakness developed. The blood count was normal and the blood sugar was 127 mg. per cent. Separation of the coronal suture was noted on x-ray examination of the skull. The results of cerebrospinal fluid examinations are recorded in table 2. Multiple cultures and smears were negative.

The patient remained quite ill, lost weight progressively, and ran a low grade fever. Multiple thoracenteses were performed to drain the left pleural effusions. Masses appeared in both flanks and the cervical lymph nodes became increasingly enlarged.

On June 5, 1936 an exploratory laparotomy was performed. Masses were found in the retroperitoneal space on both sides, that in the region of the left adrenal being the largest. Biopsy was not undertaken because of extreme vascularity. The postoperative course was characterized by further emaciation, alternate restlessness, and lethargy. The patient expired on July 4, 1936, three months after the initial symptoms. The final clinical diagnosis was neurocytoma of the adrenal with generalized metastases. Tuberculous meningitis had been considered most likely early in the course.

At autopsy there was almost complete infiltration of the mediastinum by lymphosarcoma, with invasion of the left lung and pleura. Disseminated lymphosarcoma was found in the kidneys, left adrenal, pancreas, ribs, and vertebrae. The spinal cord and brain were normal to gross inspection except for localized clouding of the leptomeninges over both occipital poles and the right cerebellar hemisphere. However, on microscopic section the pia-arachnoid of the occipital lobe, brain stem, and cervical and thoracic cord was diffusely infiltrated with lymphocyte-like tumor cells (figure 6). Throughout the parenchyma the vessels were surrounded by a cuff of tumor cells. There was invasion of the connective tissue cores of choroid tufts in the third ventricle.

Case 5.—A 29 year old housewife was admitted to the Neurological Institute on November 15, 1952 with a five week history of headache, giddiness, diplopia, blurred vision in the right eye, and tinnitus, following a head injury. General physical examination was not remarkable. On neurologic examination she was found to have no gross weakness, but there was some incoordination of fine movements. Reflexes were normal except for minimal

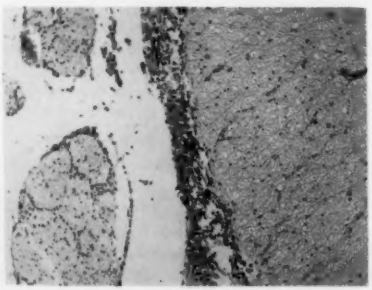


FIG. 6. *Case 4.* High-power field of thoracic spinal cord. Infiltration of pia mater, ventral roots and perivascular spaces in the parenchyma. Hematoxylin-eosin.

TABLE 3

SPINAL FLUID STUDIES — CASE 5

Date	*Lymphocytes*	*Sugar*	*Protein*	*Chloride*
1952	cu. mm.	mg. per cent	mg. per cent	mg. per cent
11/17	7,900	55	127	—
11/21	2,000	20	250	702
11/22	2,800	23	—	—
11/28	3,000	16	—	—
12/3	2,700	16	—	—
12/9	4,800	28	125	—

hyperactivity of the tendon jerks in the left upper extremity. Sensation was intact. Visual fields were normal on confrontation. There was papilledema in the right fundus but the left was normal. The extraocular movements and pupils were normal. Corneal reflexes were diminished. There was a minimal right facial weakness, but the remaining cranial nerve functions were intact. There was mild nuchal rigidity.

Blood and urine studies were within normal limits. Fasting blood sugars were 108 and 127 mg. per cent. The erythrocyte sedimentation rate was 24 mm./hr. By fluoroscopy a non-pulsatile anterior mediastinal mass was outlined. Turbid cerebrospinal fluid, often described as "ground glass" in appearance, was withdrawn on numerous occasions. Results of analyses are given in table 3. Multiple cultures were negative.

Her course was characterized by low grade fever, unaffected by penicillin and streptomycin. She complained constantly of severe headache and became restless and confused. Bilateral papilledema, right lateral rectus weakness, and mild right hemiparesis appeared. A diagnostic trial of roentgen therapy to the mediastinum (1425 r in air) resulted in disappearance of the previously noted mass. It was decided to treat the patient for probable disseminated lymphoma although pathologic proof was lacking. In mid-December she was transferred to Francis Delafield Hospital for further roentgen therapy.

By December 29 a total dosage of 1000 roentgens in air had been given to each side of the skull. There seemed to be slight improvement in her strength and mental state. Within a few days, however, profound weakness of all extremities, particularly the legs, had appeared. This was accompanied by areflexia. There was a severe loss of position and vibration sense in all extremities, but superficial sensation was grossly intact. Two courses of 10 mg. each of tri-ethylene melamine were followed by slight increase in strength.

After about 11 weeks of hospital stay, the bilateral papilledema led to decreased visual acuity, and eventually complete blindness resulted. An incomplete left oculomotor nerve palsy appeared. The quadriparesis continued to be severe and there was persistent evidence of mild organic mental abnormality.

In an effort to locate a cerebral mass for proposed biopsy, a ventriculogram was performed on February 17, 1953. The roentgen films were essentially normal. The ventricular fluid contained 4000 red blood cells, 12,000 leukocytes (all lymphocytes), 313 mg. per cent protein, 37 mg. per cent sugar, and 113 meq./l chloride. Smears and cultures were negative. A histologic preparation contained numerous neoplastic cells of the lymphocytic series.

The patient responded poorly following the procedure and died within a few hours.

At autopsy there was widespread lymphosarcoma, involving the mediastinal and abdominal lymph nodes extensively, and the liver, spleen, and kidneys to a lesser degree. On gross examination of the brain no localized masses were found. There was a terminal intraventricular hemorrhage. The leptomeninges of the base and of the spinal cord were opaque and slightly thickened (figure 7). In microscopic sections there was heavy tumor cell infiltration of the leptomeninges, cranial nerves, and spinal roots. Collars of tumor

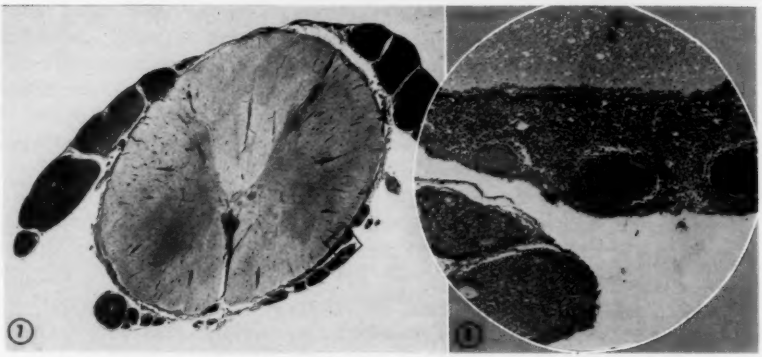


FIG. 7. *Case 5.* Cross-section of lumbar spinal cord. Enlargement of nerve roots and distention of subarachnoid space as a result of tumor invasion. Hematoxylin-eosin. FIG. 8. *Case 5.* Highly-magnified view of an area similar to that demarcated in figure 7.

cells surrounded small blood vessels in the parenchyma of the central nervous system (figure 8).

Comment: It should be mentioned in this discussion of the lymphoma group that the development of meningeal symptoms and hypoglycorrhachia in such patients (those with Hodgkin's disease in particular) will probably indicate a complicating infection by cryptococci[36] more often than meningeal spread of the neoplasm.

MELANOMA

Despite the voluminous literature on primary and metastatic diffuse melanomatosis of the leptomeninges, only three cases with cerebrospinal fluid glucose determinations could be found. The cases of Boyd[37] and Fatzer[38] had levels of 50 and 49 mg. per cent respectively. These are probably to be considered as normal, although no blood sugar levels were given for comparison. Wortis and Wortis[39] described a patient in whom disseminated melanoma developed, probably from a primary lesion in the orbit. Multiple nodules were present in the brain, but the meninges themselves were not described. The cerebrospinal fluid sugar content was 25 mg. per cent. Through the courtesy of the authors, the autopsy protocol of this case has been re-examined. The leptomeninges were described as thickened and, indeed, were infiltrated by melanoma.

OTHER DIFFUSE TUMORS

A tumor apparently of pineal origin, which spread widely throughout the leptomeninges, resulted in lowering the cerebrospinal sugar level to 20 mg. per cent, a value confirmed by repeated lumbar punctures.[40] A malignant thymoma, reported by Danisch and Nedelmann,[41] which spread through the subarachnoid space was accompanied by a "considerably reduced value" for sugar in the cerebrospinal fluid, although the exact level was not given.

Biemond's case[42] showed diffuse spread through the basal and spinal leptomeninges of a quite cellular, apparently malignant tumor. Although the author thought this was probably a "primary sarcoma of the leptomeninges," he implied that the tumor could not be accurately classified. The spinal fluid contained 12 and 18 mg. per cent glucose. In the same report Biemond indicated he had seen other cases of "meningeal sarcomatosis" accompanied by hypoglycorrhachia, but no details were given.

Of uncertain origin also is this case of diffuse tumor from our files:

Case 6.—A 54 year old man was admitted to the Presbyterian Hospital on January 31, 1925. He had complained of severe frontal headaches for about six months. Mood changes and vomiting had appeared shortly after the headaches. For three weeks drowsiness had been present.

On examination the patient was restless and completely disoriented. There was a mild right hemiparesis with slight right hyperreflexia but normal plantar responses. Sensation appeared to be intact. Nystagmus on lateral gaze was the only abnormality noted on testing the cranial nerves.

Fluid removed by lumbar puncture on February 2 was clear and contained 20 white cells per cu. mm., 97 per cent lymphocytes, 1+ globulin, and a glucose content of 30 mg. per cent. On February 28 the fluid was again clear, but xanthochromic. There were 180 cells per cu. mm., 90 per cent lymphocytes, 4+ globulin, and a sugar content of 65 mg. per cent. On later examinations the findings in the cerebrospinal fluid were similar in regard to cellular and protein content, but unfortunately no other determinations of cerebrospinal fluid sugar were made. Cultures were negative. Blood sugar determinations were not performed.

During his seven-week hospital stay the patient's confusion and restlessness increased. The only change in neurologic status was the appearance of nuchal rigidity and positive Kernig's sign. On March 3 and 13 trephinations and inspections of the dura were performed with negative results. The patient died on March 18, 1925. Clinical diagnoses of pachymeningitis hemorrhagica and encephalitis were considered.

At autopsy there was thickening and opacity of the leptomeninges over the base of the brain and around the spinal cord. There were no gross lesions demonstrable on section of the brain. Microscopically there was a layer of neoplastic cells in the pia-arachnoid of the base of the brain, cerebellum, and spinal cord. The cells were irregular in shape and contained bizarre nuclei which were either round or elongated. Occasional cells were multinucleated. Further description read as follows: "Connective tissue stains, especially silver carbonate, show that the connective tissue reticulum does not divide them up into alveoli but runs irregularly among the cells. No fibers corresponding to fibro-glia were seen. The tumor cells are not stained by Cajal's gold chloride-sublimate stain . . . . " The final diagnosis was sarcomatosis of the pia, although it was recognized that some such tumors are really gliomatous in nature. (The slides are no longer available for study.)

Doubtful cases: A number of other reports[43–46] in the older literature recorded the association of cerebral tumors and hypoglycorrhachia. The pathologic data were insufficient to establish the presence of widespread leptomeningeal metastases and/or to rule out complicating infection.

DISCUSSION

Review of the literature and study of the Presbyterian Hospital files have revealed only 46 acceptable instances of diffuse leptomeningeal tumor having cerebrospinal fluid sugar levels recorded. Of these cases, 33 (72 per cent) had cerebrospinal fluid sugar contents below 40 mg. per cent. The largest

single group is that of meningeal carcinomatosis. In this group a spinal fluid sugar content below 40 mg. per cent was found in 15 out of 19 cases.* The other groups are too small for accurate analysis. However, there are some indications that in the glioma and connective tissue groups hypoglycorrhachia is more apt to occur with the malignant varieties, such as the glioblastoma, medulloblastoma, and meningeal sarcoma, than with astrocytoma or diffuse tumors composed of mature meningothelial cells.

Various theories have been advanced to explain the hypoglycorrhachia. Cerebrospinal fluid leukocytosis and alterations in osmotic relationships due to increased cerebrospinal fluid protein have been blamed. These can be eliminated easily by the observation that normal or reduced sugar values may be seen with normal or elevated cell counts and with normal or elevated protein levels (table 4). Furthermore, there is no correlation between cerebrospinal fluid sugar and chloride contents. The imposing theory that the "blood-brain" or "blood-cerebrospinal fluid" barriers are mechanically blocked by tumor cells, thus interfering with the transfer of glucose, cannot be refuted on the basis of evidence available. Nor can conclusive physiologic evidence be adduced in its favor, however. Such approaches must await studies of cerebrospinal fluid sugar origin, exchange, and departure by the isotope technique.

Utilization of sugar by rapidly-growing tumor cells in contact with the subarachnoid space would seem to be the most plausible explanation available. Evidence indicating accelerated glycolysis by malignant cells has been reviewed by Greenstein[54] and more recently by Zamecnik.[55] An analogy is readily drawn to the situation of bacterial meningitis, wherein hypoglycorrhachia is usually ascribed to bacterial utilization.[12] However, the recent work of Goldring and Harford,[56] attacking the problem on a quantitative basis, raises serious doubt that bacterial utilization alone is sufficient to account for the low sugar values.

In brief, the mechanism of hypoglycorrhachia in diffuse meningeal disease of neoplastic (as well as infectious) origin is unknown.

This deficiency in our knowledge does not detract from the clinical importance of the observations, however. A reduced cerebrospinal fluid sugar level in the presence of any of the following syndromes – increased intracranial pressure, meningeal irritation, organic mental changes, multiple cranial nerve or spinal root signs – may be taken as evidence for the presence of diffuse meningeal tumor when infection is unlikely or ruled out. Conversely, when central nervous system tumor is suspected or one of the above clinical syndromes is observed, the level of spinal fluid sugar should be determined to establish the diagnosis of diffuse meningeal neoplasia.

*The cases of Strange mentioned previously would increase the total cases of carcinomatosis to 26, of which 21 manifested hypoglycorrhachia. Likewise, the total number of diffuse neoplasms becomes 53, of which 39 (74 per cent) were accompanied by hypoglycorrhachia.

TABLE 4

CEREBROSPINAL FLUID IN PUBLISHED CASES OF DIFFUSE MENINGEAL TUMOR

Author	*Date*	*Diagnosis*	*Sugar* (mg.%)	*Cells* (cu. mm.)	*Protein* (mg.%)
Scholz[13]	1905	Ca. stomach	"absent"	—	190
Heinemann[14]	1911	Ca. stomach	"negative"	"increased"	—
Wiechmann[47]	1925	Ca. lung	19	—	—
Moorehead & Wigham[48]	1926	Ca. ?primary site	"absent"	"increased"	—
Munch-Petersen[49]	1932	Ca. lung	24	4	—
Brodersen[15]	1935	Ca. stomach	48	16	—
Dixon, et al.[16]	1946	Ca. stomach	44 & 51	8 & 11	350 & 600
Dixon, et al.[16]	1946	Ca. stomach	34	50–750	50–140
Hamrick & Mason-Hohl[50]	1948	Ca. breast	37	0	20
Madow & Alpers[51]	1951	Ca. lung	25	2	304
Ramse[52]	1951	Ca. stomach	20	170	—
Cabot Case[18]	1951	Ca. stomach	82	75	83
Jacobs & Richland[17]	1951	Ca. stomach	27–54	15	70–90
Jacobs & Richland[17]	1951	Ca. ?primary site	46	0	40
Dodge, et al.[3]	1952	Ca. stomach	0(!)	62	50
Dodge, et al.[3]	1952	Ca. pancreas	20	16	280
Dodge, et al.[3]	1952	Ca. lung	25 & 28	49	25
Dodge, et al.[3]	1952	Ca. breast	3 & 2.5	18	375
Cabot Case[53]	1952	Ca. lung	10 & 28	50 & 82	500 & 166
Rindfleisch[1]	1904	Medulloblastoma	"absent"	—	"elevated"
Batten[19]	1908	Medulloblastoma	"absent"	—	—
Guillain & Verdun[21]	1911	Glioblastoma	"absent"	"few"	"increased"
DeLange & Smid[22]	1925	Astrocytoma (?)	"absent"	"few"	"increased"
Marcuse[23]	1943	Glioblastoma	59 & 68	2	—
Adson, et al.[24]	1952	Astrocytoma	65	6	160
Berg	1953	Glioblastoma	10–37	0–7	140–3700
Berg	1953	Glioblastoma	78	10	5000
Berg	1953	Malignant ependymoma	16 & 28	300 & 400	80
Top & Brosius[31]	1937	Primary meningeal	75 & 107	290 & 25	—
Lichtenstein & Ettleson[30]	1937	Primary meningeal	81	26	—
Marburg, et al.[29]	1943	Primary meningeal	30 & 67	10 & 20	—
Bronfman & Reumont[2]	1947	Primary meningeal	21 & 44	2 & 290	580
Bronfman & Reumont[2]	1947	Primary meningeal	22 & 28	400	72
Critchley & Greenfield[32]	1930	Myelogenous leukemia	19	0	"elevated"
Serebrjanik[34]	1933	"Lymphogranuloma"	54	360	1700
Schwab & Weiss[33]	1935	Lymphatic leukemia	33–78	280–10,000	100–522
Cabot Case[35]	1946	Malignant lymphoma	120	0	125
Berg	1953	Lymphosarcoma	27–46	2200–6500	107–330
Berg	1953	Lymphosarcoma	16–55	2000–7900	125–250
Boyd[37]	1925	Melanoma	50	280	increased
Wortis & Wortis[70]	1936	Melanoma	25	11	112
Fatzer[38]	1951	Melanoma	49	2	480
Danisch & Nedelman[41]	1928	Thymoma	"reduced"	2450	—
Friedman & Plaut[40]	1935	Pinealoma	20	3100	400
Biemond	1946	Unclassified	8 & 12	58 & 150	256 & 320
Berg	1953	Unclassified	30 & 65	20–180	increased

CONCLUSIONS

1. Diffuse, malignant tumors of the leptomeninges, whether carcinoma, glioma, sarcoma, lymphoma, or melanoma, may be expected to be accompanied by an abnormally low cerebrospinal fluid sugar content in the majority of cases.

2. The mechanism of the hypoglycorrhachia is unknown, although utilization of glucose by tumor cells probably plays a role.

3. This association carries implications of diagnostic importance.

4. There are indications for the determination of cerebrospinal fluid sugar levels in syndromes other than those of suspected infectious etiology.

ADDENDUM

Three reports of hypoglycorrhachia in a total of four additional cases of diffuse meningeal neoplasm have been noted following completion of this manuscript. G. F. Meissner's two cases (Cancer 3:313, 1953) had meningeal carcinomatosis of gastric origin. That cited by A. L. McQuown and L. I. Tyler (Am. J. Clin. Path. 23:78, 1953) was one of diffuse medulloblastomatosis. The case of C. T. Liu and G. Selbach (J. Neuropath. & Exper. Neurol. 12:186, 1953) was demonstrated to have a diffuse meningeal neoplasm of uncertain type, perhaps a sarcoma.

Therefore, the cerebrospinal fluid sugar content has been below 40 mg. per cent in 43 out of 57 cases described in the literature as diffuse meningeal neoplasm. The revised incidence of abnormality, then, is 75 per cent.

The author wishes to express his appreciation to Dr. H. Houston Merritt for his advice in the preparation of this study, and to Dr. Abner Wolf for his guidance in the analysis of pathologic material.

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Management of Chromophobe Pituitary Adenoma

Carl F. List, M.D.

THE idea that diagnosis and treatment of chromophobe pituitary adenoma are matters of easy routine must be discarded as schematic oversimplification. On the contrary, the successful management of these lesions requires not only a correct diagnosis, but also detailed and precise knowledge of the following factors: 1) size of the adenoma and its extent in relation to neighboring structures, 2) neurologic deficit, 3) endocrine status, and 4) histologic behavior of tumor.

Size and anatomic relationship of a pituitary adenoma cannot be accurately determined by clinical signs, but only by morphologic methods such as roentgenographic examination.

The osseous changes of the sella, so clearly shown by plain roentgenograms, give no reliable information concerning the true dimensions of the tumor, yet the soft tissue shadow of a large intrasellar mass is well outlined by an air-containing sphenoidal sinus. An enlarged sellar entrance does not necessarily indicate suprasellar extension nor does a normal sellar entrance preclude such possibility. Roentgenographic studies of the skull base should be supplemented by special submentobregmatic and optic foramen projections. Furthermore, anteroposterior tomograms—taking frontal sections through sella and middle fossa—are valuable for the diagnosis of asymmetric sellar and parasellar erosion. Even though pineal displacement suggests intracranial extension of the adenoma, it may be a misleading finding if a pituitary tumor happens to coexist with another unrelated expanding intracranial lesion.

Cerebral pneumography and angiography are the only means of accurately demonstrating an intracranial extension and, therefore, are essential before treatment is attempted. In the past these diagnostic procedures have been often considered superfluous, but according to recent observations[1] their informative value exceeds by far their disadvantages. Air studies clearly silhouette the intracranial portion of the tumor against the basal cisterns and third ventricle (figures 1, 2, and 3). Ventriculography is indicated when a large

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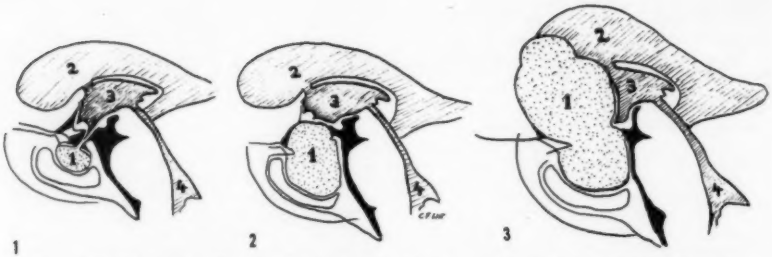

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FIGS. 1–3. Comparative diagrams showing relationship of normal hypophysis and of pituitary adenomas (stippled) to the basilar cisterns (solid black) and the ventricular system (hatched). Pituitary gland or tumor, 1; lateral ventricle, 2; 3rd ventricle, 3; 4th ventricle, 4.

FIG. 1. Note large chiasmatic and interpeduncular cisterns, the supra-optic and infundibular recesses of the 3rd ventricle in a normal individual. FIG. 2. A pituitary adenoma with moderately sized suprasellar extension compresses and elevates the floor of the 3rd ventricle. Chiasmatic cistern is partially obliterated. FIG. 3. A pituitary adenoma with large suprasellar (sub-frontal) extension compresses and displaces the anterior (and inferior) portion of the 3rd ventricle and produces a filling defect in the floor of the anterior horn. The basilar cisterns are almost obliterated.

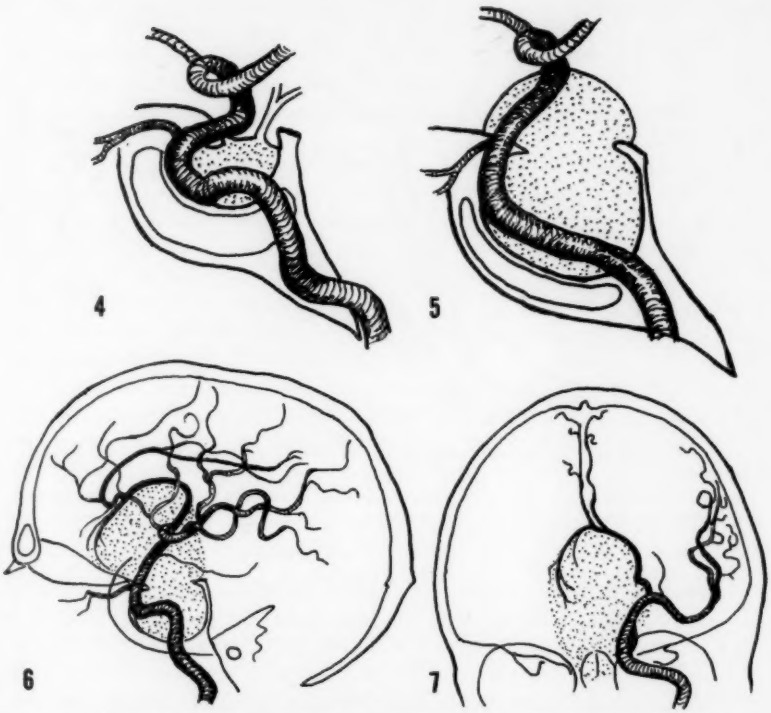
intracranial mass is suspected; otherwise pneumoencephalography is preferable when no such lesion is presumed to be present. Here again, tomograms may be helpful.

The operability of large suprasellar tumors depends upon their relationship not only to the third ventricle, but also to the circle of Willis. Arteriography gives precisely that desired information (figures 4, 5, 6, and 7).

Signs of neurologic deficit often are surprisingly slight in chromophobe adenoma. The visual pathways are usually affected at an early stage, yet may occasionally escape demonstrable damage. The nerves of the cavernous sinus frequently show no loss of function at all, even when completely surrounded by tumor. Since large intracranial extensions may not produce warning signs, the electroencephalogram is a welcome adjunct and may indicate the presence of an intracranial mass prior to the use of pneumography or angiography.

The endocrine status of the patient should be determined[2] before any case of chromophobe adenoma is treated. Pituitary tumors interfere with the important neurohumoral control system of the "pituitary-adrenal axis," and, therefore, the organism may be incapable of tolerating conditions of stress such as an operation. An adequate assay of endocrine functions includes the following investigations: basal metabolic rate, blood cholesterol, glucose tolerance, Kepler water test, blood sodium and potassium, eosinophile responses to Adrenalin and ACTH, and urinary 17-ketosteroids.

Finally, the histologic behavior of the adenoma must be studied. Unusually fast growth rate, judged by development of symptoms, and extensive irregular infiltrative destruction of the base of the skull suggest adenocarcinoma. Spontaneous vascular changes such as hemorrhage or infarction occur occasionally in pituitary adenomas.[3] They produce dramatic clinical symp-



FIGS. 4–5. Diagrams showing arteriographic appearance of the internal carotid artery and its branches in relation to a normal pituitary gland (figure 4) or to a large pituitary tumor (figure 5).

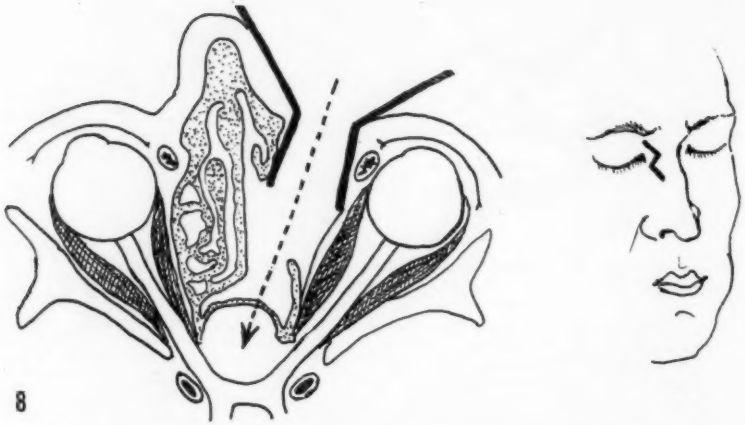
FIG. 4. Note the typical S curve of the carotid siphon in the normal arteriogram. FIG. 5. In a pituitary adenoma with suprasellar and parasellar extension; the carotid siphon is stretched to a wide arch and the supraclinoid portion is elongated.

FIGS. 6–7. Arteriograms of a very large adenoma with suprasellar extension (comparable to that shown in figure 3). The anterior cerebral artery is markedly displaced and elevated.

FIG. 6. Lateral projection. FIG. 7. Anteroposterior projection.

toms such as sudden blindness, extraocular palsies, coma, signs of intracerebral and subarachnoid hemorrhage, and finally, severe acute panhypopituitarism. The significance of these critical developments must be promptly recognized if the patient's vision or even his life is to be saved. Angiography is useful here to differentiate the condition from bleeding intracranial aneurysm.

The main objectives in the treatment of chromophobe adenoma are relief of headache and preservation or restoration of vision. Treatment of increased intracranial pressure rarely poses an urgent problem and improvement of endocrine symptoms, though desirable, cannot always be accomplished to a satisfactory degree.



FIGS. 8–9. Diagram of the transsphenoidal pituitary operation by anterolateral (orbito-ethmoidal) approach.

FIG. 8. Horizontal section through the head demonstrates the surgical exposure. FIG. 9. Shows the small Z-shaped incision near the inner canthus.

In the past 40 years, various forms of treatment have alternatingly gained and lost popularity. For instance, the transsphenoidal operation, advocated many years ago by otorhinologists,[4] was later completely superseded by the intracranial operation promoted by the neurosurgeons.[2,4,9] More recently, even some neurosurgeons prefer roentgen ray therapy to operative intervention, and, indeed, the favorable results obtained by high voltage irradiation may in the future widen the indications for roentgen therapy.[10] Evidently no single method can be considered a panacea, but the type of procedure must be carefully chosen according to the requirements of the individual case. In general it may be stated that roentgen therapy, with its slow action and low risk, may be advisable if the time element is not essential. Surgery, however, offers the chance of an immediate and decisive result at a higher risk when delay would be hazardous.

Before the tumor is attacked locally, the patient's endocrine state must be balanced to meet the stress situation induced by surgery or irradiation. Preoperative doses of ACTH (or CTH) must be considerably increased immediately after operation and roentgen therapy. In the past, the importance of hormonal support was not realized and some of the unexplainable deaths following hypophyseal operations were undoubtedly caused by acute panhypopituitarism. Not only can such disaster be prevented, but more radical surgery has now become possible with the aid of ACTH and CTH. Of equal importance is the maintenance of an adequate electrolyte balance.[11]

The following suggestions are made in regard to local therapy:

1. If a moderately-sized, entirely intrasellar chromophobe adenoma produces no clinical signs other than headaches and amenorrhea, roentgen therapy certainly is the treatment of first choice. Transsphenoidal operation may be considered only in younger individuals without complicating disease, if irradiation fails.

2. If a large intrasellar tumor has protruded into the sphenoidal sinus and caused early and minor visual symptoms, roentgen therapy may be tried first, yet cases of this type are ideally suited for the transsphenoidal operation. Most neurosurgeons have condemned the transsphenoidal approach unjustifiably, although it has been highly successful in the hands of Hirsch[3] and Cushing.[4] The objections to the method – namely, unfamiliar exposure, danger of meningeal infection, and inadequate removal of tumor – are not valid if the cases are properly selected.

Instead of Hirsch's transseptal approach, operation through the orbit and anterior ethmoids, as advocated by Chiari[12] and Smith,[13] is technically simpler, the operative field is less deep, and exposure excellent (figures 8 and 9). In the sitting position, this operation is bloodless and can be completed in less than one hour.

3. Chromophobe adenomas of moderate size with small suprasellar, rarely parasellar, extension represent the "textbook" type which is associated with the chiasmal syndrome. These lesions are best dealt with by transfrontal intracranial approach, preferably by anterolateral extradural exposure. Roentgen therapy is permissible as method of second choice, when the visual symptoms are mild; but if they fail to improve, surgery should not be delayed too long.

4. Tumors with large intracranial extension require intracranial operation, provided they are still deemed operable. The lesion is intradurally exposed through a large frontal or frontotemporal flap, after partial resection of the frontal lobe or temporal pole. At times, section of a nonfunctioning optic nerve or chiasm, or division of one anterior cerebral artery may facilitate removal, but tumor tissue adherent to the hypothalamus is better left behind.

5. If a vascular accident in a pituitary adenoma – pituitary apoplexy – has caused sudden blindness and extraocular palsies, immediate intracranial operation is mandatory, provided signs of severe panhypopituitarism are absent.[2,3] If, however, severe panhypopituitarism dominates the clinical picture, only hormone therapy should be given; surgery is contraindicated and roentgen therapy should be postponed until the endocrine condition is stabilized.

Since it is rarely desirable, nor even possible, to remove a pituitary adenoma completely, the surgical results may be improved upon and made more lasting by postoperative roentgen therapy, but irradiation should be deferred in order not to precipitate a pituitary crisis. Postoperative substitution therapy with ACTH, CTH, thyroid, testosterone, and so forth must be continued for a long time and possibly increased when additional irradiation is given.

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Perhaps there is no one feature which is more constant in the history of the malady (migraine) before us than its hereditary character, and none which so forcibly confirms its claim to be regarded, in the majority of instances, as an idiopathic affection, or which links it more closely to the natural family of neuroses.

Patients constantly tell me that it is "a family complaint;" "my mother and sisters suffer in just the same way," and so forth. By hereditary character then, I understand a family tendency or predisposition whether manifested in a direct line between parents and children, or collaterally among brothers and sisters; I have but seldom taken account of such a predisposition among more distant relatives—uncles, aunts, or cousins—not that it is unimportant, but because it is generally difficult to obtain trustworthy information about them.

The frequent existence of an inherited tendency to the more severe forms of headache did not escape the notice of our countryman, Willis. In a chapter on headache, including megrim, he refers to a "vicious or weak constitution of the affected part" as the chief predisposing cause of the malady, and this, he adds, is "sometimes innate and hereditary, as appears from hence, that the disease is often handed down from parents to children."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Experimental Intracisternal Injection of Polymyxin B

Its Role in the Treatment of Septic Meningitis

Paul Teng, M.D. and Balbina A. Johnson, B.A.

THE TOXICITY of antibiotics for the central nervous system does not run parallel wth their general toxicity. Penicillin, for instance, can be given in enormous doses intravenously or intramuscularly, with no untoward effect except an allergenic reaction in certain individuals. However, when administered directly to the central nervous system, it may cause convulsions.[1–3] The intramuscular dosage of bacitracin, on the other hand, is limited by its nephrotoxicity, but when administered directly to the central nervous system it is the least toxic among all known antibiotics used by this route.[4] Toxicity is only of major importance when it precludes the use of a drug in amounts necessary to obtain favorable therapeutic results. This study, which was done in the summer of 1951, deals with the toxicity of polymyxin B (Aerosporin) for the central nervous system and the determination of a safe dose for the intrathecal or subarachnoid injection. The methods used and the results observed are herewith presented.

METHODS AND MATERIALS

Eleven normal adult dogs were used in this experiment (table 1). Under intravenous Nembutal anesthesia, 60 mg. per 5 lbs. of body weight, and with the dog lying on its side, the cisterna magna was punctured by means of a 22-gauge lumbar puncture needle. The needle was left in place for five to eight hours until the conclusion of each experiment.

Nine dogs who received injections of polymyxin B into the cisterna magna were divided into three groups. The polymyxin B was dissolved in physiologic saline, the amount of which was kept constant for all three groups, with concentration of polymyxin B varied. Of the first group of three dogs, one received 40,000 units and the other two, 50,000 units each. The second group consisted of two dogs who received 10,000 units. The four dogs in the third

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group were injected with 5,000 units. Two additional dogs were used as controls, and received 1 cc. of physiologic saline without polymyxin B. In both the experimental dogs and controls, the amount of injected solution (1 cc.) was further diluted to 3 cc. with the cisternal fluid before it was slowly instilled into the cisterna magna. The injection took from 10 to 15 seconds. The injected antibiotic was removed from a stock solution, 500,000 units in 10 cc. of physiologic saline, pH 6.

TABLE 1

RESULTS OF INTRACISTERNAL INJECTION OF POLYMYXIN B IN DOGS

	Number of Dog	*Body Weight* (lbs.)	*Polymyxin B Dosage*	*Result*
Group 1	1	22	40,000 units	Died, 4th day
	2	33	50,000 units	Died, 3rd day
	3	35.2	50,000 units	Died, 6th day
Group 2	4	20.5	10,000 units	Weakness in hind legs lasted 22 days
	5	21.5	10,000 units	Persistent weakness in both hind legs
Group 3	6	19	5,000 units	Normal
	7	19	5,000 units	Normal
	8	23	5,000 units	Normal
	9	25	5,000 units	Normal
Controls	10	20	Control	Normal
	11	19	Control	Normal

Factors such as blood pressure, pulse rate, respiration, body temperature, and the muscular tonicity of the neck and limbs were recorded 15 minutes before and at different intervals after the intracisternal instillation of polymyxin B.

OBSERVATIONS

Blood pressure. The systolic and diastolic blood pressures of each dog were measured from the femoral artery 15 minutes before and at hourly intervals after the intracisternal injection of polymyxin B. In both the controls and the injected dogs, in spite of the difference in dosage, there were no significant changes in blood pressure, respiration, or pulse.

Body temperature. Rectal temperature was taken 10 minutes before and at two-hour intervals after the intracisternal injection of polymyxin B. In every animal except the two controls, there was a transient rise in body temperature two to three hours after the injection. The rise ranged from 1° to 4° F. and lasted six to eight hours. Twelve hours after the intracisternal deposition of polymyxin B, the rectal temperature of all dogs was normal except in the three dogs of group 1. These dogs received a large intracisternal dose of polymyxin B (40,000 to 50,000 units) and became paralyzed. Their temperatures remained at 103° and 105° F. until death, which occurred between the third and the sixth day after the intracisternal instillation.

Cerebrospinal fluid. At the end of one, two, three, four, five, and eight hours after the intracisternal injection of polymyxin B, 2 cc. of the cisternal fluid were removed for microscopic examination from each dog except numbers 8 and 9. No subsequent removal of the cisternal fluid was made in these two animals. The amount of polymyxin B (5,000 units) was left in the subarachnoid space for later microscopic study of its effect on the tissue of the central nervous system.

TABLE 2

CELL COUNT OF THE CEREBROSPINAL FLUID AFTER INTRACISTERNAL INJECTION OF POLYMYXIN B IN DOGS

Dog No.	*Dosage of intracisternal polymyxin B*	*Cell count before injection*	C.S.F. CELL COUNT AFTER INJECTION					
			1 hr.	*2 hrs.*	*3 hrs.*	*4 hrs.*	*5 hrs.*	*8 hrs.*
1	40,000 units	4	36	670	1,160	*	2,360	1,600
2	50,000 units	0	568	2,300	1,900	4,340	6,140	*
3	50,000 units	1	487	1,120	5,500	3,600	11,200	7,400
4	10,000 units	0	40	300	2,400	*	4,300	*
5	10,000 units	0	30	190	1,860	1,980	3,100	1,920
6	5,000 units	0	130	99	1,110	*	3,400	2,000
7	5,000 units	1	83	70	490	1,450	2,700	1,630
8	5,000 units		No examination					
9	5,000 units		No examination					
10	Control	0	5	4	7	*	5	
11	Control	1	2	3	3		3	

*Blood in C.S.F., specimen not examined.

The intracisternal administration of 5,000 to 50,000 units of polymyxin B was definitely irritating and invariably caused changes in the cerebrospinal fluid. One hour after injection, the number of white blood cells in the cisternal fluid began to increase. The count varied from 36 to 568 per cu. mm. Two or three hours after injection, the cerebrospinal fluid began to display a definitely cloudy appearance. The cell count varied from 490 to 5,500 per cu. mm. The highest figure was 11,200 polymorphonuclear leukocytes per cu. mm. five hours after the intracisternal injection of 50,000 units of polymyxin B (table 2, dog 3). All specimens collected after the fourth hour of intracisternal injection coagulated rapidly.

The cisternal fluid of the control animals showed no significant change, an increase of no more than 7 white blood cells three and five hours after the intracisternal injection of 1 cc. of physiologic saline which had been further diluted with 2 cc. of the spinal fluid.

There were no convulsions, muscular twitchings, vomiting, neck rigidity, or extension of the limbs in any of the nine experimental and two control dogs during the acute stage of the experiment.

Twenty-four hours after intracisternal injection, the dogs in group 1, to whom 40,000 or 50,000 units of polymyxin B had been given, were found

extremely ill, lying on their sides, but able to raise their heads and wiggle their tails although unable to stand or to sit. Weakness was found to be more marked in the hind legs than in the forelimbs. Nevertheless, there was no sensory change or disturbance of the urinary or rectal sphincters. The tongues were swollen and protruded. The dogs refused to take food or water but were able to swallow when forced. One died on the third, one on the fourth, and the other on the sixth day after the injection.

The dogs in group 2, in whom 10,000 units of polymyxin B were injected into the cisterna magna, showed weakness in the hind legs, unsteady gait, and frequent falls. These findings lasted 22 days in one dog, and the other showed the same degree of weakness until it was killed four weeks later. No sensory change could be demonstrated by the pin pricking test of the hind paws.

Group 3, consisting of four dogs who received 5,000 units of polymyxin B by the intracisternal route, showed no abnormal neurologic findings. All dogs looked normal.

The control animals also were normal.

The dogs which had survived the experiment and the controls were killed with intravenous sodium Nembutal four weeks after the intracisternal injection, and a complete autopsy was performed in each case.

Autopsy findings. Consolidation was found in the lower part of both lower lobes of the lungs in dog 1 who died on the fourth day after intracisternal injection of 40,000 units of polymyxin B. The brain and the spinal cord and their coverings were found markedly congested, with some exudates seen at the base of the brain, the ventral aspect of the brain stem, and the cisterna magna. The brain, spinal cord, and the meninges of dogs 2 and 3 showed severe congestion. In the latter dog consolidation was also found in the right lower and middle lobe of the lung. Both these animals received 50,000 units of polymyxin B by the intracisternal route; one died three days and the other six days after the injection. However, the lung pathology, hypostatic pneumonia, was probably a result of the paralysis which followed intracisternal injection of polymyxin B. There were no abnormal findings revealed in the other eight dogs, including the controls. In each case the brain, spinal cord, cauda equina, and meninges were removed and fixed in 20 per cent formalin solution.

Microscopic examination. Appropriate blocks were taken from various portions of the cerebral cortex and white matter, corpus striatum, thalamus, hypothalamus, midbrain, pons, medulla, cerebellum, many levels of the spinal cord, and cauda equina roots. The blocks were embedded in paraffin, cut at 5 to 6 microns and stained by the hematoxylin-eosin method. When indicated special stains for myelin sheath or axone were employed.

The sections of the brain, spinal cord, and the leptomeninges of the three dogs in group 1 showed severe inflammatory changes, with polymorphonuclear and mononuclear leukocyte infiltration of the leptomeninges covering the brain stem and the upper cervical cord, the base surface of the brain as well as the interfolial sulci of the cerebellum. Some fibrinous exudate was also found

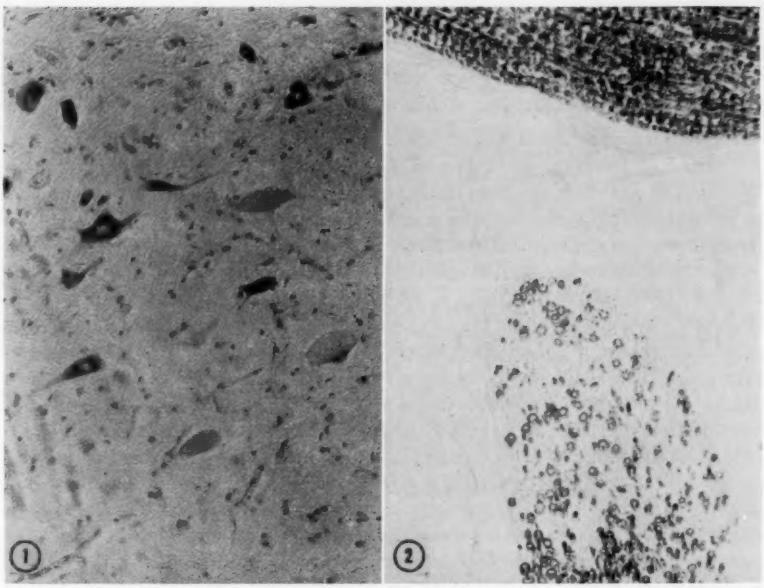

FIG. 1. Chromatolysis of the anterior horn cells of the dorsal spinal cord. Dog 4, one month after the intracisternal injection of 10,000 units of polymyxin B. Nissl's stain.

FIG. 2. Marked demyelination of the nerve roots of dog 5, one month after the intracisternal injection of 10,000 units of polymyxin B.

here and there in the above mentioned areas. The perivascular spaces of occasional blood vessels penetrating into the superficial portion of the parenchyma of the brain and spinal cord showed infiltration by polymorphonuclear leukocytes. Similar changes were also present over the thalamus and hypothalamus, as well as the ependyma of the fourth ventricle.

The cervical and dorsal segments of the spinal cord of dog 4 (group 2), who had shown transient weakness in the hind legs after the intracisternal injection of 10,000 units of polymyxin B, showed demyelinization and swollen axones in the peripheral area and chromatolysis in some of the anterior horn cells (figure 1). However, there was no decrease in the number of these cells. These changes were found more marked in the spinal cord of dog 5 (also group 2), especially in the dorsal and lumbar segments. This animal had shown persistent weaknesss in the hind legs after the intracisternal instillation of 10,000 units of polymyxin B. Demyelinization of the cervical, dorsal, lumbar, and sacral nerve roots was found in both dogs. The lumbar and sacral nerve roots were more markedly involved than those of the upper segments (figure 2).

The brain and spinal cord of the controls and the four dogs in whom

5,000 units of polymyxin B had been injected into the cisterna magna showed no significant changes.

INTRATHECAL INJECTION OF POLYMYXIN B IN CLINICAL TREATMENT OF SEPTIC MENINGITIS

The above experiment has shown that 50,000 units of polymyxin B by the intracisternal injection is toxic and fatal to dogs weighing between 22 to 35.2 lbs. In our opinion, this dosage by the subarachnoid route should not be used clinically under any circumstance in order to prevent damage to the central nervous system of the patient. Our lack of clinical experience in the treatment of septic meningitis with this antibiotic prevents us from concluding that 10,000 to 15,000 units is an adequate dosage for an adult patient. However, we feel strongly that this dosage should be tried first before any substantial increase. The amount of cerebrospinal fluid in a normal adult varies from 100 to 150 cc. Therefore, immediately following the subarachnoid instillation of 10,000 to 15,000 units, a concentration of 100 units per cc. of the cerebrospinal fluid would be attained. If the causative organism of meningitis is susceptible to this concentration of antibiotic, this proposed intrathecal dose once or twice a day, supplemented with intramuscular injections, might be able to control the infection. Recently we have observed two patients with septic meningitis treated with polymyxin B. Both patients, one a newborn and the other an adult, had been given an intrathecal dose of 50,000 units of polymyxin B. This dosage produced toxic reactions in both cases, consisting of convulsions in one and urinary difficulty in the other. Both patients survived the infection. A brief history of these patients is presented to illustrate the toxicity of a large intrathecal dose and the safety as well as the adequacy of a smaller dose in the treatment of septic meningitis.

Case 1.—A 40 hour old male infant, weight 7 lbs. and 10 oz., had peritonitis resulting from a congenital stenosis and perforation of the lower ileum. A resection and an end-to-side anastomosis of the lower ileum was performed on the third day of life. Postoperatively, he was given 1,000,000 units of penicillin intramuscularly and 100 mg. of streptomycin intravenously for one day. On this day he had one episode of opisthotonus and spasticity of the limbs which lasted a few hours. Otherwise his condition was considered satisfactory. Twenty-four hours later, instead of penicillin and streptomycin, he was treated with intramuscular Terramycin, 200 mg. a day continued for five days. Thereafter the intramuscular Terramycin was displaced with oral Terramycin of the same dosage for nine succeeding days. It was stopped because of repeated vomiting. The infant did well for five days without any antibiotic therapy. The following day his temperature rose to 100° to 101° F. He coughed and had some nasal discharge. Therapy with 400,000 units of Crystacillin a day was started and was continued for four days. In spite of this therapy the infant became lethargic, and his temperature remained at 100° to 101° F. His color was pale, and there was a slight spasticity of the limbs and opisthotonus. At times his respirations were found to be rapid. However, the fontanelle was not full and the neck was soft.

The next day a lumbar puncture yielded pus from the subarachnoid space. Cultures of both blood and cerebrospinal fluid grew an *E. coli* which was found to be sensitive to streptomycin 2 mcg./ml., Terramycin 2.0 mcg., Chloromycetin 2.0 mcg., and polymyxin B 1.5 units. Treatment was started immediately with streptomycin, 40 mg. every six hours

intramuscularly, and sodium sulfadiazine, 5 per cent solution, 14 cc. by subcutaneous infusion. The next morning Chloromycetin, 100 mg. every six hours by intramuscular injection, was added to the therapy, and one 10-mg. intrathecal injection of streptomycin, together with 3,000 units of streptokinase was given. The condition of the patient became worse, he was more lethargic, and the opisthotonus was more marked. Twenty-four hours later the intrathecal dose of streptomycin was reduced to 5 mg. with 3,000 units of streptokinase a day for four succeeding days, and the systemic treatment with sodium sulfadiazine, Chloromycetin, and streptomycin was continued with the dosages as mentioned above, except that the subcutaneous sodium sulfadiazine varied from 5 to 8 cc. daily. In spite of this treatment, there was no sign of clinical improvement. The daily cerebrospinal fluid cultures remained positive for *E. coli* although his temperature had become normal.

On the seventh day after the discovery of the meningitis intrathecal streptomycin was displaced with polymyxin B, 5 mg. (50,000 units) with additional intramuscular injections of the same antibiotic, 2.5 mg. every six hours. Following the intrathecal instillation, the infant developed several episodes of generalized convulsions involving the left side of the body more than the right. A second intrathecal injection of polymyxin B of the same dose was given the following day. After this injection the patient became stuporous, with frequent convulsions. During the intervals between convulsions the left side of the body twitched constantly. Therefore, polymyxin B was stopped on the third day of treatment. Nevertheless, the cerebrospinal fluid and blood culture had become sterile and remained so from the day following the initial intrathecal dose of polymyxin B. On this day, a ventricular tap was done; the fluid was clear and contained 299 white blood cells, and culture revealed no growth. The urine showed one plus albumin and 5 to 7 white blood cells per high power field at the end of polymyxin B therapy; it became normal a week later. Nonprotein nitrogen was 23 to 32 mg. per cent. The episodes of convulsions and muscular twitchings continued for five days and were finally controlled with Dilantin and phenobarbital. The infant gradually became alert and his general condition improved slowly.

Treatment with streptomycin was stopped on the sixteenth day, polymyxin B on the third, and Chloromycetin and sodium sulfadiazine on the twenty-first day. The infant made a complete recovery and was discharged when he was two months old. Neurologic examination showed no abnormal findings. He was seen one month later and was considered to be a normal baby.

Comment. This case illustrates that 5 mg. (50,000 units) of polymyxin B to a newborn of 7 lbs. and 10 oz. given by the intrathecal route is an excessive dose. In the first section of this paper it was demonstrated that the intracisternal instillation of this dose in experimental dogs having three times the body weight of this patient caused the death of all animals. However, this infant survived and showed no abnormal neurologic signs except convulsions and stupor, which were acute toxic reactions to the intrathecal instillation of polymyxin B. This case also illustrates the effectiveness of polymyxin B against an *E. coli* infection of the meninges which had not responded to previous combined antibiotic therapy. In spite of repeated intrathecal injections of streptomycin, 5 mg. daily for five days, cultures of the cerebrospinal fluid had remained positive. Yet after the first intrathecal injection of polymyxin B, the cerebrospinal fluid became sterile and remained so. The toxic reaction which has been observed in this patient is a serious one and should be avoided by using a smaller intrathecal dose.

Case 2.—A 29 year old man, weight 214 lbs., had a radical mastoidectomy done on the left side for cholesteatoma seven years previously, following which he had a draining ear. Six months before admission a craniotomy was performed for removal of the intra-

cranial portion of the cholesteatoma. The present admission was for treatment of the ear infection and frequent dizzy spells. Culture of the discharge from the left ear showed a *Ps. aeruginosa* which was sensitive to streptomycin, Terramycin, and polymyxin B. It required 12 units (1.2 mcg.) of the latter antibiotic to inhibit the growth of the organism. Shortly after admission the mastoid wound was re-explored and the wound was packed daily with streptomycin-soaked dressings. Following the operation cerebrospinal fluid was seen leaking through the wound, and he was given prophylactic Terramycin, 250 mg. every eight hours, and streptomycin, 2 gm. daily. This leakage continued. Ten days later the patient suddenly developed a severe bilateral headache, associated with chills, nausea, and vomiting. His temperature was 102.5° F., pulse irregular, and neck stiff. A lumbar puncture was performed and yielded cloudy cerebrospinal fluid with an initial pressure of 280 mm., 140,000 white blood cells, 35.7 mg. per cent of sugar, and 131 mg. per cent of total protein. No organism was seen on direct smears, and repeated cultures of the cerebrospinal fluid showed no growth. He was immediately given one injection of Crystacillin, 800,000 units. The following day culture of the wound was reported as a *Ps. aeruginosa*, a staphylococcus, and a streptococcus. This time the *Ps. aeruginosa* was found to be resistant to streptomycin but still sensitive to Terramycin and polymyxin B. The latter two organisms were susceptible only to bacitracin. Therefore, therapy with penicillin, streptomycin, and Terramycin was stopped, and the patient was given sulfadiazine, 1 gm. every four hours by mouth, and polymyxin B, 60 mg. every eight hours by the intramuscular route. He was mentally cloudy and restless. Otherwise, his condition remained unchanged. Ten hours later 50,000 units of polymyxin B were instilled into the lumbar subarachnoid space. Following this intrathecal injection, the patient developed severe pain in the back and urinary retention necessitating catheterization for the next five days.

It is our opinion that the cerebrospinal fluid cultures were false negatives, probably resulting from the previous systemic antibiotic therapy. Because there was a direct communication between the cerebrospinal fluid and the infected wound, it was decided to treat the patient for septic meningitis with a smaller intrathecal dosage of polymyxin B and bacitracin. Ten thousand units each of these antibiotics were injected into the lumbar spinal canal the next day. This was supplemented with intramuscular polymyxin B, dosage as above mentioned, and bacitracin, 25,000 units every eight hours. Two days later this combined intrathecal treatment was stopped, at which time the cerebrospinal fluid contained 775 white blood cells per cu. mm. His temperature was 100° F., and he was more alert and less restless than before. The mastoid wound was dressed daily with a solution containing 1,000 units of bacitracin per cc. and 0.1 per cent of polymyxin B. Leakage of cerebrospinal fluid through the wound ceased on the second day of polymyxin therapy. At this time the mastoid wound was again explored and no pus pocket was found. Following this exploration the patient was given a prophylactic intrathecal injection of bacitracin and polymyxin B, 10,000 units each. The systemic medication with polymyxin B, bacitracin, and sulfadiazine was stopped on the third day after the second operation. His temperature was normal and stayed so two days later. The urine showed 1 to 10 white blood cells, occasional granular casts, and 0.08 to 0.4 gm. albumin per 1,000 cc. during the course of polymyxin B and bacitracin therapy. Nevertheless, the urine was normal a week later. The mastoid wound became clean and was dressed daily with polymyxin B and bacitracin solution for two and a half weeks until complete healing was achieved. The patient was discharged on the thirtieth day of hospitalization in good condition and showed no disability or paralysis.

Comment. Although causative organisms were not recovered from the cerebrospinal fluid, infection of the leptomeninges and of the cerebrospinal fluid in this case can hardly be doubted. The cerebrospinal fluid was in direct communication with the infected mastoid wound from which a *Ps. aeruginosa*, a staphylococcus, and a streptococcus were repeatedly cultured. The former

was sensitive to Terramycin and polymyxin B, and the latter two organisms were susceptible only to bacitracin. The infection was rapidly controlled by combined therapy with polymyxin B and bacitracin which were administered both by the intramuscular and by intrathecal routes. The initial intrathecal instillation of 50,000 units of polymyxin B had caused retention of urine and pain in the back, and the patient had to be catheterized for five days.

Septic meningitis caused by mixed organisms of Gram-negative bacillus and Gram-positive coccus is usually fatal. In past years we have encountered four cases of septic meningitis of this type, and this patient is the only one who has survived; this we believe was due to the combined intrathecal therapy with bacitracin and polymyxin B.

DISCUSSION

Like penicillin, streptomycin, and bacitracin, the subarachnoid or intrathecal instillation of polymyxin B is definitely irritating to the central nervous system.[1–4] For clinical use by this route, the dosage of each particular antibiotic has to be carefully calculated in each individual case. Experiments have shown that intracisternal injection of 50,000 units of polymyxin B in three dogs of 22 to 35.2 lbs. of body weight produced a fatal outcome in every instance. Ten thousand units caused paresis of the hind legs with corresponding degenerative changes in the lumbar spinal cord. Intracisternal injection of 5,000 units was well tolerated, however, with no abnormal neurologic signs.

Bryer et al.[5] injected polymyxin D (B-17) intrathecally in dogs and observed that 10,000 units caused no untoward reaction, while 50,000 units was followed by a transient paresis of the hind limbs which disappeared in 24 hours, and the administration of 100,000 units produced a similar muscular weakness which cleared completely over a period of ten days. The polymyxin which they used in their experiment was dissolved in 2 cc. of buffered saline, pH 7.4, and further diluted with 2 cc. of cerebrospinal fluid. It was given over a period of 5 to 10 minutes. Swift and Bushby[6] injected 10,000 units of polymyxin E in 0.5 cc. of normal saline or distilled water into the cisterna magna of rabbits and produced no neurologic toxic signs, although there was a moderate pleocytosis. Repeating the dose daily for three days did not increase the number of cells, and 24 hours after the last dose the number of cells in the cerebrospinal fluid had dropped from 4,000 to 6,000 per cu. mm. to 100 to 200. Doses of 30,000 and 50,000 units given by the same route caused coma, convulsions, and death in two of the three animals. The third dog showed general muscular weakness.

Polymyxin B does not readily pass through the normal blood-brain-barrier and reaches the cerebrospinal fluid only in an insignificant concentration. However, when the meninges are damaged, as in the case of septic or aseptic inflammation, a considerably higher level of this antibiotic can be obtained. Nevertheless, the subarachnoid deposition of polymyxin is rapidly absorbed into the blood circulation and thence excreted through the kidney. Twenty-four hours after the intrathecal injection of 10,000 units of this antibiotic,

TABLE 3

SUMMARY OF RECORDED CASES TREATED WITH POLYMYXIN

Author (Year)	*Age of patient*	*Type of meningitis*	*Other intrathecal antibiotic used*	*Polymyxin*	*Intrathecal polymyxin dosage and number of injections*	*Result*
Kagan, 1949 [7]	13 mos.	H. influenzae		B	1 mg., 1 injection; 3.5 mg., once daily, 5 days	Recovery
Brakeley, 1950 [8]	3½ yrs.	H. influenzae	Streptomycin, 25 and 50 mg., once daily, 2 days	B	1 mg., once; 3.5 mg., once daily, 3 days	Recovery. Unsteady gait 7 weeks
Hayes & Yow, 1950 [9]	17 yrs.	Ps. aeruginosa	Dihydrostreptomycin, 50 mg. daily, 7 days; 100 mg. daily, 12 days	B	2 mg., twice daily, 15 days	Recovery. Nausea and vomiting, pain in legs and back following injection
Tomlin, 1951 [10]	35 yrs.	Ps. aeruginosa	Penicillin, 10,000 units, once	B	5 mg., once daily, 3 days	Recovery. Pain in legs, perineal anesthesia lasted "several days"
Swift & Bushby, 1951 [6]	9 mos.	H. influenzae	Penicillin, 25,000 units, 9 injections	B	0.5 mg., one day; 1 mg., daily, 7 days; 1.5 mg., daily, 4 days	Recovery
Swift & Bushby, 1951 [6]	9 mos.	H. influenzae	Penicillin, 50,000 units, 3 injections	E	2.5 mg., daily, 2 days; 3.75 mg., daily, 13 days	Died
Swift & Bushby, 1951 [6]	18 mos.	H. influenzae	Penicillin, 25,000 units daily, 10 days	E	3 mg., daily, 11 days; twice daily, 6 days	Recovery
Swift & Bushby, 1951 [6]	3½ yrs.	H. influenzae	Penicillin, 25,000 units daily, 7 days	E	6 mg., daily, 3 days; twice daily, 5 days	Recovery. Hypotonia of legs for 6 weeks
Swift & Bushby, 1951 [6]	2½ yrs.	H. influenzae	Penicillin, 2,500 units, once	E	4 mg., daily, 2 days; twice a day, 4 days; 3 mg., daily, 2 days	Recovery. Hypotonia of legs for 3 mos., flat-foot
Swift & Bushby, 1951 [6]	33 mos.	H. influenzae		E	4 mg., 4 injections in 3 days; once daily, 2 days; 2 mg., daily, 2 days	Recovery
Swift & Bushby, 1951 [6]	22 mos.	H. influenzae		E	4 mg., twice daily, 2 days; once daily, 2 days	Recovery
Swift & Bushby, 1951 [6]	34 mos.	H. influenzae		E	4 mg., twice daily, 2 days; once daily, 4 days	Recovery
Ebsworth & Leys, 1951 [11]	2 wks.	E. coli	Streptomycin, 20 mg. once	B	2 mg. daily, 5 days	Recovery. Hypotonia of legs, 6 mos.
Jawetz, 1952 [12]	2½ yrs.	Ps. aeruginosa	Streptomycin, 25 mg. (shock), once	B	5 mg., daily, 4 days; every other day, 2 to 3 wks., relapse: again daily, 3 days; every other or 3rd day, 4 wks.	Recovery
Jawetz, 1952 [12]	No detail		No detail		No detail	Recovery. Internal hydrocephalus
Authors	40 hrs.	E. coli	Streptomycin, 10 mg. once; 5 mg., daily, 4 days; streptokinase, 3,000 units daily, 4 days	B	5 mg., daily, 2 days	Recovery. Repeated convulsions
Authors	29 yrs.	Ps. aeruginosa, staphylococcus, streptococcus	Bacitracin, 10,000 units daily, 4 days	B	5 mg., once; 1 mg. daily, 5 days	Recovery. Retention of urine, 5 days. Pain in the back

Equivalent: 1 mg. = 10,000 units; 1 mcg. = 10 units.

1+ unit per cc. could still be recovered from the cerebrospinal fluid.[6] After the breach of the blood-brain-barrier as a result of the subarachnoid injection of the antibiotic, the drug re-enters the subarachnoid space from the blood. In the case of meningitis, 12, 24, or even 32 hours after intrathecal instillation of the antibiotic, an adequate therapeutic level can usually be demonstrated in the cerebrospinal fluid. This is probably due to the antibiotic traversing the blood and the cerebrospinal fluid circulation. The subarachnoid deposition first exerts a local action of high concentration of the instilled drug on the cerebrospinal fluid space, and its rapid absorption into the blood circulation would then produce a systemic effect. Therefore, antibiotic treatment by this route is a local-systemic medication.

To date in the medical literature there are 17 recorded cases of septic meningitis treated with polymyxin including the two herein reported (table 3).[6–12] Various dosages of intrathecal polymyxin have been used in these patients ranging in age from newborn to 35 years. The causative organisms were *Ps. aeruginosa, E. coli, H. influenzae*, or mixed bacteria. Of these 17 cases, including one which was not described in detail,[12] eight showed neurologic toxic reactions to the intrathecal injection of polymyxin, 16 recovered, and one died. Two newborns with *E. coli* meningitis were treated with an intrathecal dosage of 2 mg. and 5 mg. of polymyxin, respectively. One developed weakness in both legs and the other had repeated convulsions. Two patients under the age of one year were treated for *H. influenzae* meningitis. One recovered after receiving repeated intrathecal injections of 1.5 mg. of polymyxin and showed no untoward reaction. The other, who was treated with combined intrathecal injections of 2.5 to 3.75 mg. of polymyxin and 25,000 to 50,000 units of penicillin, died. Three patients between one and two years of age were treated with 1.5 to 4 mg. of polymyxin, and all recovered without showing untoward reaction to the intrathecal medication. Four patients between two and three years of age were given a 4- to 5-mg. dose by repeated intrathecal injections. One developed weakness of the legs lasting three months and a permanent flat-foot condition. Two patients of three and a half years of age, one given 3.5 mg. and the other 6 mg., both developed weakness in the legs with unsteady gait lasting six and seven weeks respectively. A 2- to 5-mg. dosage was used in one adolescent and two adult patients. All showed neurologic symptoms, perineal anesthesia, retention of urine, or pain in the legs and back immediately following each intrathecal instillation. In conclusion, four patients to whom only intrathecal polymyxin was given showed no neurologic toxic reaction. Of 12 patients in whom intrathecal streptomycin and/or penicillin had also been used prior to or accompanying the intrathecal instillation of polymyxin, one died, eight showed toxic neurologic signs (table 3), and three had no reactions.

This review indicates that toxic symptoms have been caused by a minimal dosage of 2 mg., and the maximal dose that has not produced any untoward symptoms was 5 mg. Retention of urine, perineal sensory disturbance, pain in the lower limbs or back, hypotonia of legs, unsteady gait, and convulsions are

Equivalent: 1 mg. = 10,000 units; 1 mcg. = 10 units.

serious neurologic complications following intrathecal deposition of polymyxin. These reflect damage to the spinal cord, the cauda equina, or their roots. Thus, these toxic reactions should not be dismissed as insignificant.

Whenever intrathecal polymyxin is indicated, as in the case of septic meningitis caused by susceptible organisms, a carefully calculated small but adequate dosage should be used in order not to cause injury to the central nervous system, unless this small dosage proves to be inadequate. The subarachnoid injection of penicillin, streptomycin, or polymyxin B is toxic to the central nervous system and its use should be reserved as the last resort. When indicated, as in the case of septic meningitis, only the proper antibiotic should be chosen as revealed by laboratory sensitivity tests of the causative organism. From the study made on the experimental dogs and from analysis of a small series of reported cases, the following dosage is proposed based upon the age of the patient (table 4).

TABLE 4

PROPOSED DOSAGE OF POLYMYXIN B FOR INTRATHECAL INJECTION

Age in years	*Dosage of polymyxin B*
Newborn to 6 months	500 to 1,000 units
6 months to 1 year	1,000 to 2,500 units
1 year to 5 years	2,500 to 5,000 units
5 years to 10 years	5,000 units
10 years to adolescence	5,000 to 10,000 units
Adult	10,000 to 15,000 units

Equivalent: 1 mg. = 10,000 units; 1 mcg. = 10 units.

SUMMARY

1. Polymyxin B is irritating and toxic to the central nervous system when injected into the subarachnoid space. Three dogs died after intracisternal injection of 40,000 to 50,000 units of polymyxin B. Two dogs showed weakness in the hind legs with unsteady gait after the injection of 10,000 units by the same route. The injection of 5,000 units into the cisterna magna in four dogs caused no untoward symptoms.

2. Degenerative changes have been found in the spinal cord of two dogs with paralytic hind legs after the intracisternal instillation of 10,000 units of polymyxin B. These animals were killed one month after the injection.

3. Two cases of septic meningitis, one caused by an *E. coli* and the other by a mixture of organisms, were treated with intrathecal polymyxin B. In the latter case intrathecal bacitracin was also used. Both patients recovered from the infection. One developed repeated generalized convulsions and the other had transient retention of urine as a result of the intrathecal injection of 50,000 units of polymyxin B.

4. In a review of 17 cases of septic meningitis treated with intrathecal polymyxin, the minimal dosage that has caused toxic reaction was 20,000 units;

maximal amount that has not produced untoward symptoms was 50,000 units.

5. The intrathecal dosage of polymyxin B, determined according to the age of the patient, is proposed.

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A fit of epileptic type may leave paralysis, very rarely general, commonly of one-half of the body, or of still smaller range, affecting a limb only. The form and nature of the paralysis differ essentially in different cases, and by many writers the varieties have not been distinguished. The first and most common is transient weakness, incomplete in degree, passing away in the course of a few hours, but usually recurring after other attacks, and, therefore, probably of "functional" nature, and a direct result of the attack. The second form is that in which paralysis succeeds the first fit, or first series of fits, and persists for weeks or months or permanently, irrespective of the subsequent convulsions. These are cases in which the paralysis is the result of an organic lesion of the brain, of which the convulsions are also the consequence. They are, for the most part, cases of "post-hemiplegic convulsion." The third class are those in which persistent paralysis follows a fit in a confirmed epileptic. In these cases, which are extremely rare, a cerebral hemorrhage has probably resulted from the vascular strain during the fit.

The rarity of cases of the third class renders them of small practical importance. I have never met with an example of this form. The second class, "post-hemiplegic convulsions," will be considered separately. The first form, the transient paralysis, which is apt to recur, alone needs consideration among the conditions after attacks.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Stimulation of the Hippocampus and Medial Cortical Areas in Unanesthetized Cats

Birger R. Kaada, M.D.,
Jan Jansen, Jr. and Per Andersen

THE GENERAL CONCEPT of most morphologists has been that the hippocampus, the entire limbic (cingular) and hippocampal gyri, and the amygdaloid nuclei are concerned with important olfactory functions. Recent anatomic and physiologic observations,[1,2,3,4,5] however, have thrown doubt upon the concept of the purely olfactory function of these parts of the forebrain and considerable interest has been aroused concerning their possible role in the regulation of autonomic activity and emotional behavior. In the present study, which has been carried out since the spring of 1951, an attempt has been made to obtain further information regarding the functional significance of these forebrain structures by stimulating them through implanted electrodes in unanesthetized animals. The results of stimulation of the amygdala will be reported in a subsequent paper;[6] the present communication deals with the hippocampus, the cingulum bundle (which is one of the important afferent projections to the hippocampus), and the cortex of the medial aspect of the prefrontal region, the limbic and hippocampal gyri from which cingulum fibers take their origin.

All the latter structures appear to be intimately interconnected (figure 1). The efferent pathway from the hippocampus, and as far as is known the only one, is represented by the fornix, which emerges as the fimbria along the border of the hippocampus and which terminates with the main mass of the fibers in the mammillary bodies. From the latter the impulses may be transmitted by way of the mammillothalamic tract (bundle of Vicq d'Azyr) to the anterior nucleus of the thalamus and thence to the anterior and posterior limbic and retrosplenial cortices. In these cortical areas the cingulum fibers originate and run through the white matter subjacent to the cortex of the retrosplenial region and hippocampal gyrus to terminate mainly in the subiculum and presubiculum of the hippocampal formation[7,8,9,10] and possibly directly in the hippocampus proper.[7] According to the recent study of Adey and Meyer,[10] a conspicuous portion of the cingulum bundle originates in the granular prefrontal cortex, mainly from its medial portion.

From the Anatomical Institute, University of Oslo, Norway.

Read at the Twelfth Scandinavian Neurological Congress, Oslo, September 13, 1952.

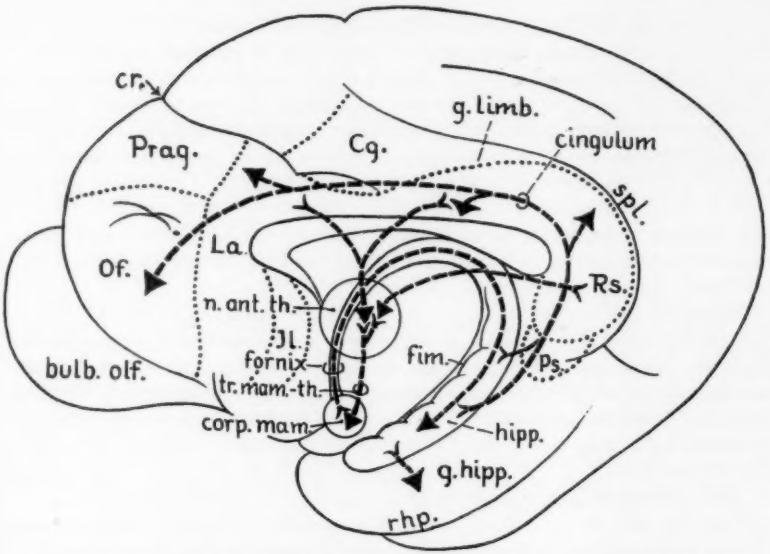


FIG. 1. Diagram demonstrating the principal fiber connections of the hippocampal-limbic system considered in the present paper. Areal division (dotted lines) on the medial surface of cat's brain according to Rose and Woolsey.[35]

Abbreviations: bulb. olf.—bulbus olfactorius; Cg.—cingular area; corp. mam.—corpus mammillare; cr.—cruciate sulcus; fim.—fimbria fornicis; g. hipp.—gyrus hippocampus; g. limb.—gyrus limbicus; hipp.—hippocampus; Il.—infralimbic area; La.—anterior limbic region; n. ant. th.—anterior thalamic nucleus; Of.—orbitofrontal region; Prag.—precentral agranular area; Ps.—postsubicular area; rhp.—posterior rhinal fissure; Rs.—retrosplenial area; spl.—splenial sulcus; tr. mam. th.—tractus mammillo-thalamicus (Vicq d'Azyr).

Papez[11] appears to be the first to postulate that the hippocampus and limbic cortex form part of such a circular pathway, and he put forward the well-known hypothesis that this morphologic system ". . . . constitute[s] a harmonious mechanism which may elaborate the function of central emotion as well as participate in emotional expression." The existence of such a circuit (hippocampus → fornix → mammillary body → anterior nucleus of the thalamus → limbic cortex → cingulum → hippocampus) has also been suggested by the anatomists, (Le Gros Clark and Meyer[12]).

PREVIOUS PHYSIOLOGIC STUDIES

Limbic cortex. Stimulation experiments have shown that complex autonomic and somatomotor effects can be produced from the anterior limbic region, but not from the posterior part of this gyrus.[5,13,14,15] Further, ablation of the anterior limbic cortex in monkeys is reported to result in profound changes in behavior.[14,16]

Hippocampus and fornix. Ablation of these structures, on the other hand, has so far not yielded any significant effects. Thus, no behavior changes fol-

lowed complete electrolytic lesions of both fornices in cats.[17] Bard and Mountcastle[18] observed, if anything, a slight increment in pleasure reactions as a result of bilateral removal of the hippocampi with the overlying neocortex in cats. Dott[19] noted no symptoms that could be ascribed to section of the fornices in one patient. More recently, Garcia-Bengochea and his coworkers[20] were not able to detect any changes in the behavior of monkeys subjected to a number of tests before and after section of the fornices. The tests employed were form discrimination, pulling-in test, concentration test, multiple objects test, reaction to animate objects, and auditory reactions. Neither does transection of the fornix or complete destruction of both hippocampi seem to interfere with olfactory discrimination tests.[21,22]

Electrical stimulation of the hippocampus and fornix in anesthetized cats and monkeys has not resulted in any significant somatomotor or autonomic responses such as overt movements, changes in spinal reflexes, respiratory movements, blood pressure, salivation, micturition, or defecation.[5] Further, Eliasson[23] noted no alterations in gastric motility following hippocampal stimulation in cats. Apposite to these observations are those of Sigrist[24] who concluded that no definite physiologic response could be related to stimulation of the mammillothalamic tract in cats, and ". . . derselbe muss daher in Tierversuch als 'stumme Zone' angesehen werden." Hunter[25] observed reactions consisting of unconsciousness and changes in behavior resembling epileptic automatism of psychomotor attacks on stimulation of the fornix in one unanesthetized cat, and of the anterior thalamic nucleus in two cats. These responses were associated with electrical after-discharges and thus represent an epileptiform manifestation.

After all these studies with essentially negative results, the physiologic role of the hippocampus and of the cortex of the hippocampal and posterior part of the limbic gyri still remains obscure. Recent studies by the evoked potential method, however, have led to the interesting disclosure that these structures receive sensory impulses of various origin. In 1936 Gerard, Marshall, and Saul[26] made the incidental observation in cats that electrical potentials in response to visual and tactile stimuli could be recorded from the hippocampus, the cortex of the limbic and hippocampal gyri, and from the amygdala. In preliminary studies Robinson and Lennox[27] and Lennox and Madsen[28] have confirmed this observation and have recorded potentials in the same structures also on acoustic stimulation. Similar responses in the hippocampus have recently also been obtained on olfactory[29,29a] and gustatory stimulation.[29a]

Thus, the hippocampus and part of the cortex of the limbic and hippocampal gyri appear to be a polysensory representation area, the functional significance of which is unknown.

PROBLEMS

The aim of the present investigation has been to determine whether any somatomotor, autonomic, or behavior responses can be elicited from the

structures in question in the unanesthetized and freely-moving animal. It has been of particular interest to study the reactions to stimulation of points from which evoked potentials of various origin can be recorded. Finally, the purpose has been to compare the responses from the structurally interconnected hippocampus, cingulum bundle, and the cortex of the limbic, hippocampal, and prefrontal areas.

MATERIAL AND METHODS

A total of 79 electrodes were implanted in 24 adult cats. Eighteen electrodes were placed in the hippocampus and fimbriae fornices, 18 in the limbic gyrus and the retrosplenial area, 13 in the cortex of the hippocampal gyrus, 11 in the prefrontal region, and four in the white matter subjacent to the posterior limbic cortex. Fifteen electrodes were placed in various other cortical areas as controls. On the first day the animals were anesthetized with a mixture of Nembutal (13 mg./kg.) and Chloralose* (30 mg./kg.) given intraperitoneally, and bipolar electrodes were implanted. These consisted of a stainless steel wire of 0.6 mm. diameter cemented together with a 0.5 mm. thick wire, both insulated except for the tips which were about 0.5 to 1 mm. apart. The electrodes were inserted through a burr hole in the dorsal calvarium, and fixed to the skull by means of a metal cup screwed into the opening and filled with a soft acrylic mass which hardened within a few minutes. In preliminary experiments the electrodes were oriented by means of the Horsley-Clarke instrument. It is difficult by this procedure (even with specially designed ear plugs) to avoid perforation of the ear drums. With some experience, however, a fairly accurate placement of the electrodes could readily be performed by hand without the use of the Horsley-Clarke coordinates, the animal's head being secured in a heavy metal holder. The electrodes were connected by thin insulated copper wires running under the scalp to plugs fixed to a collar, thus avoiding traction on the electrodes when the unrestrained animal was stimulated later.

The stimulator was of the square wave type with independently controllable frequency (0.02 to 300 per sec.), pulse duration (0.1 to 20 msec.), and voltage (0 to 25 volts). The parameters most often used were a frequency of 40 per sec., a pulse duration of 10 msec., and intensities of 2 to 6 volts for periods of 5 to 30 seconds.

While the animal was still under anesthesia the effect of stimulation on respiratory movements was studied. A corrugated gum rubber tube was fastened around the chest and the movements were transmitted in a closed air system to a Marey's tambour in connection with an ink-writing kymograph. Autonomic responses (pupillary changes, salivation, micturition, defecation, pilo-erection) and overt somatomotor movements were looked for.

The next day, when the effects of the anesthesia had worn off, the animal was placed on a table and the electrodes were connected to the output of the stimulator through thin, flexible wires hanging down from the ceiling and plugged into the animal's collar (figure 2B). The responses to stimulation were studied by three or four different observers and recorded on 16 mm. Kodachrome film.

In later experiments the animals were again lightly anesthetized with Nembutal and Chloralose in order to study the effects of stimulation of the same points on the electrocorticogram and for recording of evoked potentials. Records of the electrical activity of various cortical areas were obtained either by electrodes placed directly on the exposed surface of the brain or by electrodes screwed through the skull until they lay in contact with the dura. In some experiments the screws were inserted on the first day and electrocorticograms obtained the following day from the unanesthetized animal. The electro-

*Chloralose was kindly supplied by E. Merck, Darmstadt, and Nembutal by Abbott Laboratories Ltd.

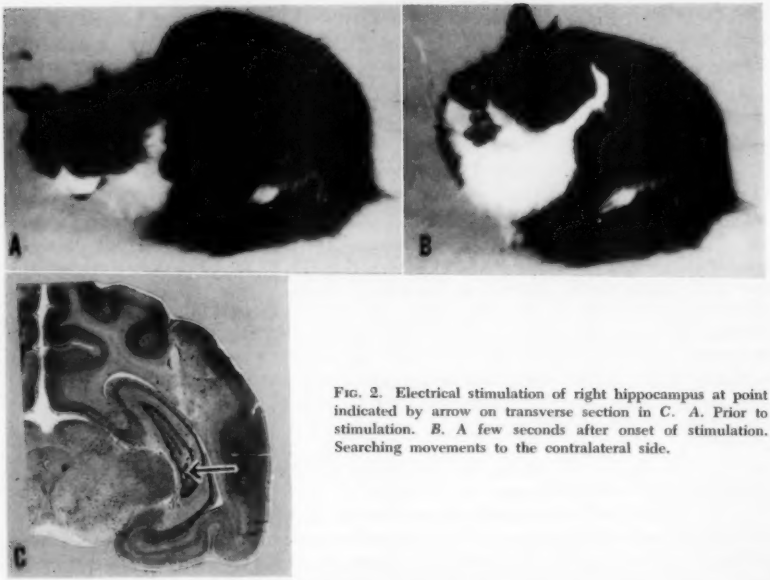


FIG. 2. Electrical stimulation of right hippocampus at point indicated by arrow on transverse section in *C*. *A*. Prior to stimulation. *B*. A few seconds after onset of stimulation. Searching movements to the contralateral side.

cortical activity was recorded bipolarly or by the average electrode technique[30] on an eight-channel Ediswan electroencephalograph. The latter was also sometimes used for recording (monopolarly) of potentials evoked in the hippocampus or in the medial and basal cortex in response to acoustic and tactile stimulation. Ordinarily, however, the evoked potentials were photographed on a cathode ray oscilloscope operating in synchrony with the stimulus.

At the end of the experiment electrolytic lesions were made at the electrode tips. The brains were fixed and serial sections (20μ thick) made, every twentieth section being stained according to the Nissl method.

RESULTS

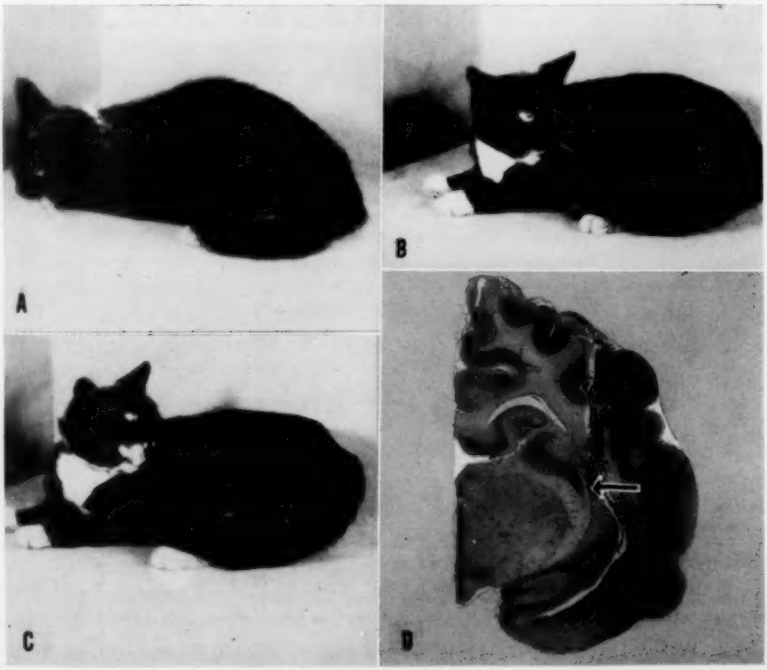
Hippocampus and fimbria fornicis.

Surprisingly constant changes in behavior were obtained in the unanesthetized animals on stimulation through the 18 electrodes found to be located in these structures. Although the responses might vary considerably in detail from point to point and from animal to animal, there were some common features which perhaps best might be described as increased "attention" or "vigilance." In the majority of the experiments this "attention" was not directed towards external stimuli intentionally produced by the observer, but it appeared as if the animal reacted to some kind of psychic experience or sensation from the environment. Immediately at the onset of stimulation all spontaneous pre-occupation such as walking or licking ceased and the facial expression changed to "attention" or alertness, perhaps associated with some

surprise, bewilderment, or anxiety. The animal usually raised its head and upper part of the body slightly (figure 2), the eyes opened, and the pupils dilated slowly; there were slight pricking movements of the ears and quick glancing or searching movements of the eyes and head, almost invariably to the contralateral side or forwards. The animal seemed to direct its attention towards "something imaginary" in the surroundings and never towards its own body as might happen on amygdala stimulation.[6]

These responses were even more striking when the animal was lying down, drowsy, prior to the stimulation. Another typical experiment is illustrated in figure 3. The electrode tip is seen to be situated in the center of the hippocampus (*D*). From this point potentials were recorded in response to acoustic stimuli (loud speaker click; record *F*) and to a tap on the leg. By electrical stimulation of this point the resting animal (*A*) suddenly appeared awake and vigilant, raised its head and ears, and looked to the opposite side (*B*). With a little stronger stimulation the cat might get up on its feet and start walking in circling movements to the opposite side, all the time making quick and anxious searching movements up into the air or, more rarely, along the floor. In some animals there were a few isolated sniffing movements, but any rhyth-

Fig. 3. Reaction of bewilderment, fear, and anger (*B* and *C*) caused by stimulating fimbria fornicis at point marked by arrow in *D*. *A*. Before stimulation.



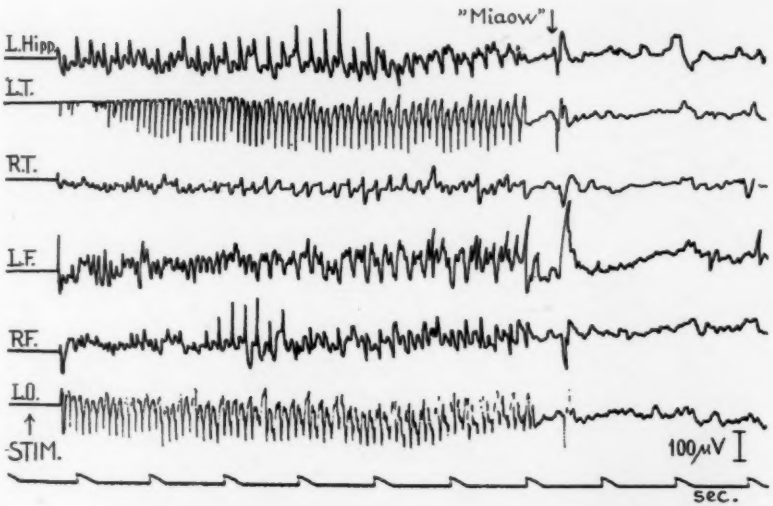
mic sniffing or licking as on stimulation of parts of the amygdaloid complex[6] were never seen on stimulation of the hippocampus.

During the period of excitation the reaction of most animals to external stimuli, such as noise or movements within their field of vision, was diminished rather than increased. The animals, however, were undoubtedly conscious, their attention being attracted and intensely fixed on the "something" which they seemed to experience. Usually a somewhat stronger external stimulation could provoke the cat to react, and it might even follow the movements of the observer. A threatening movement might cause the animal to withdraw a few steps, but the next moment it was again performing the quick and anxious searching movements to the contralateral side. A few animals appeared to be in a state of alertness during stimulation, with increased attention towards external stimuli as well.

On increasing the stimulus strength the contralateral glancing and circling movements were performed at considerable speed. Besides, several cats now showed signs of fear, anger, or fury during the stimulation, such as growling with a snapping or gnashing of the teeth (figure 4), clawing, and arching their backs. This response might occur when the animal was left alone, but particularly when disturbed by various kinds of external interference such as touch or attempts to hinder its movements. The reaction was defensive rather than aggressive in character. The animal might retire into a corner in fright, and only exceptionally did it attack the hand of the observer when approached. Two cats ran away fearfully, trying to escape after a few seconds of stimulation.

These changes in behavior could be repeated on numerous stimulations of the same point and the response was rather stereotyped for each point, but could vary for different points in the hippocampus in one and the same cat. An animal, who on the first stimulation fixed its attention towards the upper contralateral quadrant of the visual field, did so on every trial. It is further of importance to note that a given response was fairly uniform during the entire period of the passage of the current through the electrode, for instance for half a minute or more. On interruption of the current, the prestimulatory activities were soon resumed, or the response could continue for 10 to 15 seconds into the poststimulation period and then gradually subside. Frequently a few rebound licking movements around the lips were seen.

The behavior responses could sometimes, particularly at a relatively strong stimulus, continue for even longer periods after cessation of stimulation, for instance up to half a minute or more. The change to normal behavior was occasionally heralded by a miaow." These after-effects were often associated with electrical after-discharges, usually with a frequency of 6 to 8 per second, and synchronously with after-discharges in the hippocampi (figure 3). No attempts were made in this investigation to study the exact cortical distribution of the after-discharges. However, they could be recorded bilaterally over the prefrontal, posterior ectosylvian, and suprasylvian regions. During these



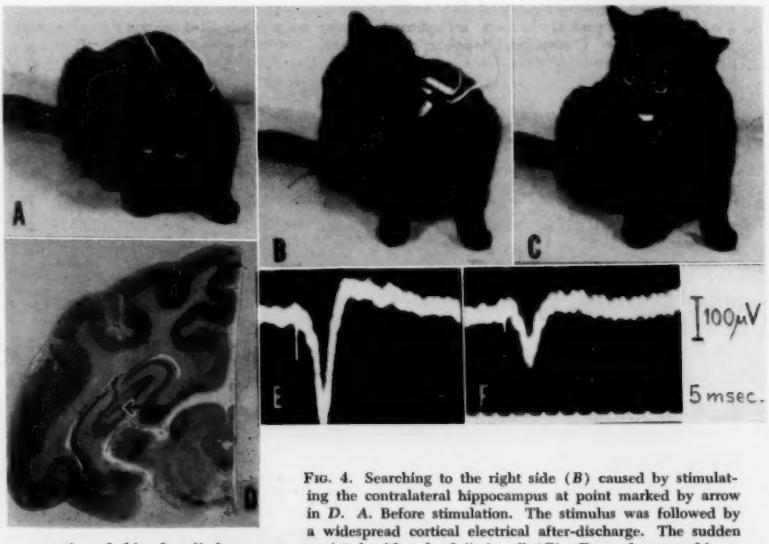


FIG. 4. Searching to the right side (*B*) caused by stimulating the contralateral hippocampus at point marked by arrow in *D*. *A*. Before stimulation. The stimulus was followed by a widespread cortical electrical after-discharge. The sudden cessation of this after-discharge was associated with a loud "miaow" (*C*). From the same hippocampal site small positive potentials were recorded in response to acoustic (record *F*) and somesthetic stimulation. Record *E* illustrates the larger potential evoked in the cortical primary acoustic area by the same acoustic stimulus.

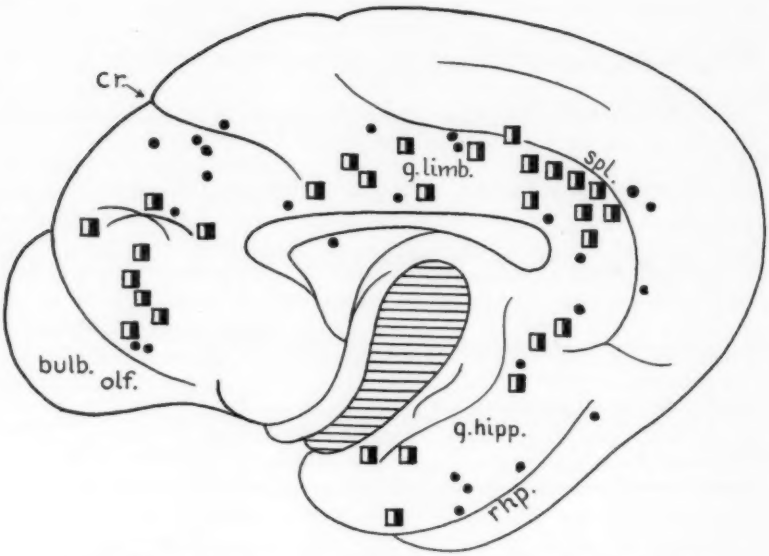


FIG. 5. Medial aspect of the cat's hemisphere indicating points (half-filled squares) from which behavior responses ("attention," searching and glancing movements to the contralateral side), similar to those produced from the hippocampus and fimbria fornices, were obtained. Dots: no such responses.

after-discharges the animals appeared less responsive or unresponsive to external stimulation. In two cats stimulation of the hippocampus by a relatively strong intensity resulted in generalized tonic-clonic convulsions.

Aside from the searching movements and the slow pupillary dilatation as part of the described behavior responses, no immediate somatomotor or autonomic effects were observed on stimulation of the hippocampus and fimbria, contrary to the effects obtained from parts of the amygdaloid nuclear complex and the rostral portion of the hippocampal gyrus (*vide infra*).

The evoked potentials will not be dealt with in this communication. It is of interest in this connection, however, to state that all types of behavior changes could be obtained from points from which either no or from which definite potentials could be recorded in response to acoustic and tactile stimulation.

Cortex of the proreate, limbic, and hippocampal gyri.

Stimulation of these structures elicited behavior responses almost identical to those produced from the hippocampus and fimbria. The location of the 46 points stimulated is indicated in figure 5, all points being transferred to the right hemisphere. Figure 6 illustrates an example of the "attention" response obtained from a point in the retrosplenial region on the border

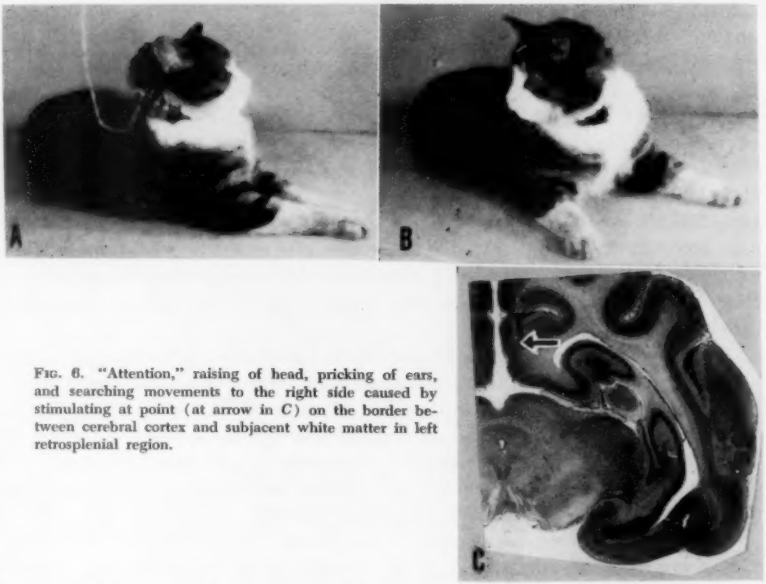


FIG. 6. "Attention," raising of head, pricking of ears, and searching movements to the right side caused by stimulating at point (at arrow in *C*) on the border between cerebral cortex and subjacent white matter in left retrosplenial region.

between the gray and subjacent white matter. No significant qualitative difference in the effects from the various areas could be ascertained. However, the signs of fear, anger, or fury were less marked on stimulation of the prefrontal and anterior limbic areas as compared to the effects obtained from the posterior limbic and retrosplenial cortex (and the subjacent white matter), the hippocampus, and fimbria. Excitation of points in the anterior limbic cortex also produced *immediate* contraversive turning of the head, tonic movements of the limbs, changes in respiratory movements, and various autonomic responses as previously reported by several authors. Similar responses were obtained from the anterior portion of the hippocampal gyrus.[6]

As on stimulation of the hippocampus, the quick glancing movements obtained from the medial cortex were almost exclusively directed towards the contralateral side. Contralateral circling movements were produced also from points in the prefrontal cortex and in the hippocampal gyrus and were usually more marked than on stimulation of the hippocampus proper.

Control stimulations through 15 electrodes placed in various other cortical areas (temporal, parietal, occipital, and sensorimotor regions on the dorsolateral and medial aspects of the hemisphere) did not produce any of the behavior responses described above.

COMMENTS

Lacking information about the animals' subjective experience during the stimulation, it is obvious that extreme caution must be exercised in any

attempts to interpret the nature of the outward manifestation of behavior change. It is difficult, from the observed behavior response, to decide whether the stimulus-activated nervous mechanisms are on "the effector side," that is, concerned with the direct motor innervation leading to that particular behavior pattern, or whether it is a secondary reaction to some kind of sensation or psychic experience, for instance to visual or acoustic impressions or to activation of memory engrams. A study of the responses to several hundred stimulations by three or four different observers has led us, however, to the tentative explanation that the animals react to some kind of sensation or psychic experience ("hallucinations"). Their behavior is, as suggested above, such as might be expected from such experience. However, only stimulation of these structures in conscious human beings might give a definite answer to this problem.

In view of the fact that the hippocampus and the cortex of the limbic and hippocampal gyri can be activated by acoustic, optic, and somesthetic stimulation, the possibility that some quality of these sensory modalities can be appreciated at this level of the central nervous system appears not unlikely. In the present study, evoked potentials in response to sensory excitation were recorded from a number of points (but not from all) yielding searching movements and other behavior responses on stimulation.

Whether the structures concerned participate in the retention or activation of engrams can similarly only be a matter of speculation at our present state of knowledge. It may be pertinent to recall, however, that severe vascular destruction of both hippocampi in one human subject has resulted in disturbances of memory as the most prominent manifestation.[31] Furthermore, according to Schlesinger,[32] tumors in the splenial region involving the medial cortex of both hemispheres cause a clinical syndrome " . . . characterized by conspicuous disturbances of memory and higher mental functions that depend upon the utilization of engrams." Finally it seems relevant to draw attention to the fact that isolated atrophy of the mammillary bodies, to which the hippocampus has its main efferent projection, has been found in patients with Korsakow's psychosis, in which disturbances of memory are among the most conspicuous phenomena.

Whatever the interpretation of the outward manifestation of behavior change, it is of considerable interest that apparently the identical type of response as that produced from the hippocampus can be obtained also from rather extensive medial cortical areas which, however, appear to be structurally connected with the hippocampus through the cingulum bundle. Also, stimulation of part of the amygdaloid nuclear complex has yielded the same type of response.[6] It is difficult to determine whether the effects obtained from the white matter of the limbic gyrus are due to activation of the cingulum bundle, or of other projections of the limbic cortex, for instance with the diencephalon and brain stem. The important question therefore arises whether the behavior change resulting from stimulating the medial cortex is dependent upon the integrity of the cingulum bundle and hippocampus, or whether the

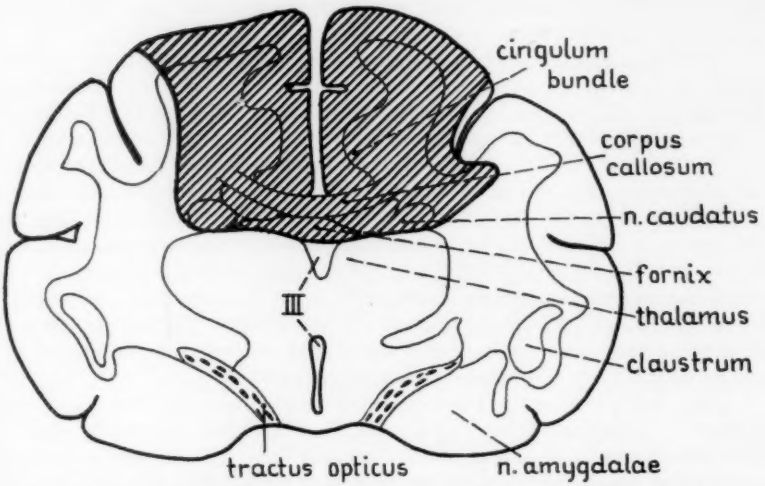


FIG. 7. Transverse section through an electrolytic lesion severing the cingulum bundle and the fornix on both sides. The "attention" response elicited by stimulating the medial prefrontal cortex on the right side remained entirely unaltered after this lesion had been made.

response rather depends upon projections to common subcortical structures from the hippocampus and from the medial areas concerned. Preliminary ablation-stimulation studies attempting to elucidate the neuronal mechanisms involved in the behavior responses in question tend to favor the latter possibility. Thus, an extensive bilateral lesion completely severing the cingulum fibers as well as the fornix in a frontal plane (figure 7) did not influence the typical searching movements obtained by stimulating the prefrontal cortex.

Quite recently Akert,[33] working in Hess' laboratory, has briefly reported on a similar type of behavior change (consisting of slow turning of the head to the contralateral side) resulting from stimulating the dorsomedial and anterior thalamic nuclei (projecting upon the prefrontal, limbic, and retrosplenial areas, respectively) and from the intralaminar nuclei of the thalamus. In view of this observation and the fact that the response has not been described in any other of the numerous studies reported in the literature on stimulation of subcortical structures in unanesthetized animals, it seems quite possible that a corticothalamic mechanism is involved. Experiments in progress in our laboratory tend to support this assumption. In this connection it is also relevant to recall the recent demonstration of direct fiber projections to the dorsomedial thalamic nucleus from the amygdala,[34] and possibly from the hippocampus.[35] The latter may also activate the anterior group of nuclei via the mammillary bodies and the mammillothalamic tract. Physiologic indication of connections from the hippocampus, amygdala, and part of the limbic and

hippocampal gyri to the thalamic nuclei in consideration has been given previously.[6, p.156-160, 238-244]

The similarity between the inadequate and stereotyped behavior change in cats and certain types of psychomotor epileptic attacks or automatisms in humans has already been emphasized by Hunter.[25] The peculiar searching movements are seen as the initial phenomenon in the majority of psychomotor seizures. It is of fundamental importance, therefore, for an understanding of the mechanisms involved in automatic states to know the origin and significance of this type of response. The present investigation indicates some of the structures which might be involved in the initial seizure discharge. The experiments further suggest that an initial searching to one side points to an initial discharge in the opposite hemisphere. Other manifestations of psychomotor attacks, such as various visceral and somatomotor phenomena, we believe to be due to activation of the amygdaloid nuclear complex, and these will be dealt with in the succeeding communication.

Addendum: During the preparation of the present paper the reports by Gastaut and associates[36,37] on hippocampus and amygdala stimulation in cats have become available. These authors have observed behavior changes similar to those herein described on stimulation of these structures. The cortex of the medial aspect of the hemispheres was not studied.

SUMMARY

1. The results of stimulation of the hippocampus and of medial cortical areas through implanted electrodes in unrestrained freely moving cats are reported.

2. Very similar and constant behavior changes were produced from the hippocampus, the medial prefrontal region, and the cortex of the limbic and hippocampal gyri (figure 5). During stimulation the animals performed quick glancing or searching movements to the contralateral side; the facial expression changed to "attention" associated with some surprise, bewilderment, and anxiety. The reaction to external stimuli was decreased, the animals' attention being intensely fixed on "something" in the environment which they seemed to experience. Some cats showed signs of fear, anger, and fury.

3. The nature of this outward manifestation of behavior change and its relation to psychomotor seizures are discussed.

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CLINICAL PATHOLOGIC CONFERENCE

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Section Editor

Presented by David B. Clark, M.D.

PRESENTATION OF CASE

A white male carpenter was first seen at Johns Hopkins Hospital in 1942 for treatment of a pterygium. In 1944, at age 60, he returned with complaints of weakness, polyuria, nocturia, and weight loss. Physical examination was remarkable only for evidences of arteriosclerosis, but fasting blood sugar was 302 mg. per cent and Benedict's test on the urine was 4 plus. He was considered to have diabetes mellitus of senile type, and a regimen of protamine zinc insulin and diabetic diet was prescribed. This controlled his glycosuria well, when diet and medication were adhered to, but he proved unreliable and tended to spill sugar frequently, always with clear evidence of dietary indiscretions.

In 1945 he developed an infection of the right hand, and was admitted to the medical wards in a state of diabetic acidosis. The fasting blood sugar was 487 mg. per cent, carbon dioxide combining power 6.9 vol. per cent. A large subaponeurotic abscess of the right palm was drained surgically. On routine treatment for his acidosis, plus penicillin, he did well and was discharged after 20 days, with instructions to continue on insulin and his previous diet.

In 1946 he began complaining of numbness and tingling in the fingers. On neurologic examination the cranial nerves were all normal, except for bilateral hearing loss of conductive type. There was weakness of all small muscles of the left hand and some weakness of dorsiflexion of the left wrist, together with a mild distal sensory loss in the hand, not clearly localizable to root or peripheral nerve distribution. The remainder of the neurologic examination was negative. X-ray of the cervical spine showed marked narrowing of the C5-C6 interspace with marked osteoarthritic changes about the lower cervical vertebrae. Examination of the blood showed no evidence of Addisonian anemia. No unanimity of opinion was ever reached as to whether the changes represented cervical root compression secondary to cervical spondylosis or a mild diabetic neuropathy. Continuous use of crude vitamin extracts gave no relief, and the complaints and signs persisted throughout the remainder of his life.

On October 25, 1952, after a 31 months' absence from clinic, he was admitted to the urology service with complaints of black stools for two years, weight loss of 20 pounds in the last two months, and dysuria for one month. On admission, his temperature was 98° F., pulse 68, respirations 18, and blood pressure 150/100. The lungs were clear to percussion and auscultation, the heart small, the tones distant and pure. The liver was palpable one finger's breadth below the costal margin, but had been so for years. The abdomen was otherwise negative. There was a phimosis and balanitis, and the prostate was enormously enlarged and rubbery to the touch; no source of the melena was apparent. Peripheral pulses, extremities, and the major reflexes were all in order. Hemoglobin was 13 gm. per cent,

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white count 8200 with a normal differential. The urine specific gravity was 1.028, reaction acid, tests for albumin negative, but there was a 4 plus reduction; only one white cell per high power field was present. Catheterization demonstrated a residual urine of 275 cc.

It was thought that he had benign prostatic hypertrophy with some retention, compensated hypertensive and arteriosclerotic heart disease, uncontrolled diabetes mellitus, and possible gastrointestinal bleeding of unexplained etiology. Drainage of the bladder with a Foley catheter was introduced, and a variety of studies were begun. Serological test for syphilis was negative. Intravenous pyelogram and cystogram revealed a spina bifida occulta, normally functioning kidneys, a large bladder with a marked prostatic filling defect, and changes in the right hemipelvis suggestive of Paget's disease. X-ray of the chest was considered negative. Cystoscopy was attempted but was not successful, apparently due to a urethral diverticulum. The electrocardiogram showed a sinoauricular rhythm, with occasional ventricular extrasystoles. The QRS complexes were consistent with left ventricular strain.

On admission, the patient stated he had been taking protamine zinc insulin, 10 units daily. Blood sugars were in the neighborhood of 300 mg. per cent on this dose, so insulin was increased to 25 units daily, which stabilized the fasting blood sugar at between 130 and 160 mg. per cent. No immediate cause for gastrointestinal bleeding was discovered, though the stool was found to have a 1 plus guaiac reaction.

On November 5, the eleventh hospital day, the patient underwent perineal prostatectomy under spinal anesthesia. A 102 gm. prostatic adenoma, which subsequently showed only hyperplasia on section, was removed. The operation was without particular event. That evening he was given 500 cc. of whole blood. His temperature rose to 102° F. and he had several shaking chills. Next day he felt well, but on November 7 serosanguineous fluid and air was expressed from the wound, and for two or three days thereafter there was note of crepitus about the wound. Beta hemolytic streptococci, streptococcus fecalis, and coliaerogenes organisms were subsequently cultured from the wound.

In the immediate postoperative period and for a few days thereafter, the patient required rather larger doses of insulin, ranging from 35 to 55 units daily. By November 11 some peculiarities in sugar levels were noted. The morning urine was commonly sugar-free, but within three hours after taking insulin as high as a 3 plus urine sugar was reported. By November 14 the fasting blood sugar had fallen to 92 on only 15 units of insulin daily, and from then on the insulin requirement decreased to zero and the fasting blood sugar drifted steadily downward. He was not comatose at any time, though he complained of occipital headache daily from about November 17 onward.

Drainage from the wound continued, but the patient remained afebrile on penicillin and streptomycin. Except for his headache, for which the ophthalmologists suggested glasses after noting the presence of retinal exudates, he seemed to do reasonably well. The blood sugar fluctuations were at first thought to be due to smuggled food, but the steady downward drift of the blood sugar soon excluded this. About November 20 he began to complain of feeling weak and nauseated. Two days later he began to vomit, and a fall in blood pressure to 98/60 was noted. On November 24 he suddenly lost consciousness, drooled saliva, and twitched about the face and left pectoral region. His temperature had risen to 102° F., pulse to 116, but respirations remained 16. He was comatose, responding only to painful stimuli. The neck was stiff. The pupils were small, regular, and reacted to light. The left arm and leg were flaccid. Plantar and abdominal reflexes could not be obtained but there was bilateral ankle clonus, and the twitching about the left shoulder persisted. The impression was that he had had a right-sided cerebral vascular accident. Laboratory studies of the blood showed glucose 32 mg. per cent, carbon dioxide combining power 26.6 vol. per cent, sodium 141.0 mEq./L., potassium 4.4 mEq./L., and nonprotein nitrogen 44 mg. per cent. While preparations for lumbar puncture were being made, the patient expired.

DISCUSSION

In brief, this is the case of an elderly man subject to diabetes which was never properly controlled over a period of eight years. In spite of this, he got into real difficulty only once on the occasion of a severe suppuration; his relative immunity to acidosis was obviously much more a tribute to the character of

his diabetes than to the fidelity of his medication. The only other possible diabetic complication, alleged neuropathy affecting the hands, is certainly open to question, since his symptoms were at least as typical of cervical root compression secondary to cervical spondylosis, for which he had x-ray evidence, as they were of diabetic neuropathy. Alternately, many of his symptoms may have been those of vascular insufficiency.

After eight years, he developed fairly clear-cut urinary difficulties secondary to benign prostatic hypertrophy, complicated by weight loss and melena. The diabetes, as usual, was out of control, and, as might be expected in an elderly diabetic in poor nutrition with depleted glycogen stores, some days were spent in bringing his fasting sugar to proper levels and reducing his glycosuria. He then withstood a perineal prostatectomy without difficulty. On the night of operation he was given a blood transfusion, after which he had a shaking chill and rise in temperature. One would expect this to be a transfusion reaction, or possibly due to a bacteremia. Since the urinary findings were rendered worthless by the operation, it is difficult to distinguish the two on that basis. On the one hand, there is no mention of urticaria, backache, or other common concomitants of a transfusion reaction, and on the other, by the second postoperative day there was clear evidence of wound infection; the weight of supportive evidence favors a bacteremia as the cause of his chill and fever.

Throughout the remainder of his life, it was obvious that there was some infection in the wound, though its systemic effects were kept in check with antibiotics. By the twelfth day he began to complain of headache; by the fifteenth, of weakness and nausea; and by the seventeenth, he began to vomit and a marked fall in his blood pressure was noted. No electrocardiogram was taken, but with his previous record and known vascular disease, a myocardial infarction is certainly a possible explanation. Two days later, he suddenly lost consciousness, with the signs of an irritative and destructive lesion of the right cerebral cortex, and expired very shortly thereafter.

If one considers only this sequence of events, the conclusion of the medical consultant who saw him terminally – that he had suffered a vascular accident – is surely the logical one. His age, vascular disease, diabetes, symptoms suggestive of a myocardial occlusion two days before death, known pelvic infection, and terminal symptoms are all consistent with a right-sided cerebral vascular accident. This could have been embolization from a mural thrombus overlying a myocardial and endocardial infarction; it could have been a spontaneous thrombosis in an elderly, ill, arteriosclerotic individual; less probably, it might even have been a cortical or dural sinus thrombophlebitis such as is seen in parturient women, with emboli, sterile or otherwise, reaching the cerebral veins via the epidural plexuses of the spinal cord. Cerebral abscess from the same source, or from infection of a silent focus of encephalomalacia at the time of his probable bacteremia, is a possibility, though a poor one in view of the short course, apoplectic onset, and relative rarity of cerebral abscess from a remote source, without some intermediate focus in the lung.

There is, however, one significant detail which argues strongly against such conclusions. This is the remarkable change which took place in the diabetes. By the sixth postoperative day, it was noted that the blood and urine sugars were showing such unpredictable swings, that for a time he was suspected of having a concealed source of food. By the

TABLE 1

Date	Urine sugar	F.B.S. mg.%	CO_2 comb. power—vol.%	Chlorides mEq./L.	NPN mg.%	Insulin
October 25	4 plus	293	27	101	33	PZI 10 U.
November 4	trace	147				PZI 25 U.
November 5	Day of operation.					
November 6	*	255				PZI 25 U.
November 10		262	25.8	94.5	37	PZI 55 U.
November 12		162				PZI 45 U.
November 14		92				PZI 15 U.
November 17		136				PZI 10 U.
November 18		80				0
November 21		100				0
November 24	(Death)	32	26.6		44	0
November 24	Serum Na 141.0 mEq./L.					
	Serum K 4.8 mEq./L.					

*Urine sugars not regularly recorded after operation, because of hematuria.

eighth day, the fasting blood sugar had fallen to 92 mg. per cent on 15 units of insulin, previously a small dose for him. From that day onward, the insulin requirement was zero and the fasting blood sugar decreased steadily (see table 1) to 32 mg. per cent at death. Such a change is a classical example of the Houssay phenomenon in man – the cure, as it were, of a pancreatogenic diabetes by destruction of the anterior lobe of the hypophysis.

The liability of diabetic patients to spontaneous thromboses in the vascular bed of the hypophysis, with resulting necrosis of the gland, has been recognized for years.[1] Necrosis of the pituitary following hemorrhage, especially in postpartum women, and leading to the relatively slow onset of symptoms of hypophyseal deficiency is also an old observation.[2,3] Less well known, perhaps, is the more sudden and dramatic change which appears, as it did here, in the diabetic who has sustained an infarction of the anterior lobe of the hypophysis. Since the first report,[4] a total of less than a dozen such cases have been described.[5] Their endocrine details belong properly to the endocrinologist. To the neurologist, the syndrome is one in which a diabetic, commonly, though not always, after exposure to some illness or added stress, begins to complain of weakness, then headache, and a cold sweat. There may be mental confusion, or periods of semistupor; if insulin administration is continued, as it often is for a time, severe hypoglycemic reactions are seen. The blood pressure drops, a degree of postural hypotension often appears, and vomiting becomes persistent. Terminally, the course, which may last from a few hours to several weeks, is marked by episodes of spontaneous hypoglycemia, coma, convulsions, and the appearance of shifting neurologic signs. In the acute case, the blood sugar is the only chemical determination to alter early or dramatically.

This patient conformed fairly closely to that clinical syndrome, and the diagnosis of an infarction of the anterior lobe of the hypophysis is surely the one of choice. It is of interest that at autopsy the gland showed not only zones of co-

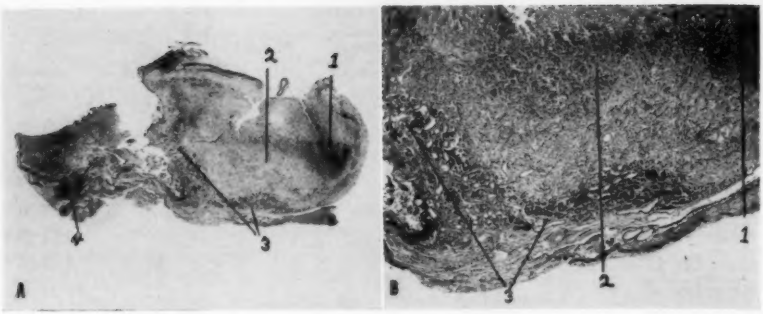

FIG. A. Midsagittal section of hypophysis. At 1, an abscess in the anterior lobe. At 2, a broad zone of coagulation necrosis. At 3, surviving cells of the peripheray of the anterior lobe, and the pars intermedia. At 4, a small abscess in the capsule of the posterior lobe.

FIG. B. Same section as figure A magnified 2½ times. Details as in figure A.

agulation necrosis, but also multiple small but histologically typical abscesses. From it were cultured several organisms, at least one and possibly two of which had previously been cultured from the drainage from the perineal wound. This, together with the mild meningeal reaction observed, suggests that a part at least of his difficulties did start with a bacteremia, presumably on the occasion of his chill. The point cannot be established with real certainty, since the parasellar sinuses were not properly examined to exclude the presence of emboli, and since there is certainly much outright infarction in the gland.

AUTOPSY

At autopsy, examination of the great body cavities was not especially revealing. The lungs were essentially normal, the heart showed marked arteriosclerosis of the coronary vessels without occlusion, scarring of the myocardium, and an old anterior infarct of the left ventricular wall. Liver, pancreas, and adrenals were grossly normal, though microscopically the pancreas showed some hyalinization of the islands of Langerhans. The bladder was thickened and trabeculated, with evidence of cystitis; the prostatic defect was filling with healthy granulations. There was a fairly marked generalized arteriosclerosis.

The brain itself and its meninges were not grossly remarkable. The vessels showed marked arteriosclerosis and intimal thickening, but there were no occlusions or softenings. On removal of the brain, a drop of white pus was noted on the diaphragma sellae. When the diaphragma was incised, the entire anterior lobe was seen to be white, semiliquid, and necrotic. On culture from the anterior lobe, hemolytic staphylococci, alpha Streptococcus fecalis, Aerobacter aerogenes, and Proteus mirabilis were obtained, though blood and other postmortem cultures were negative.

Microscopically, the meninges were sparsely infiltrated with polymorphonuclears; subependymally, especially in the third ventricle, there were small cuffs of polymorphonuclears about the vessels. In the hypophysis, almost the entire anterior lobe was necrotic, only a few cells along the capsule and in the pars intermedia surviving. In the necrotic portions, one could distinguish both zones of coagulation necrosis and small typical abscesses (figure B). In the posterior lobe, which was least involved, there

were tiny abscesses in the capsule (figure 1). No bacteria could be seen on section, and the parasellar venous sinuses unfortunately were not searched in detail for thrombi.

Final Autopsy Diagnosis: Hyalinization of islands of Langerhans and atrophy of pancreas. Generalized arteriosclerosis most marked in coronary vessels. Old myocardial infarction. Operative absence of prostate, for benign hyperplasia. Abscess, with necrosis, of anterior and posterior lobes of hypophysis. Mild purulent meningitis and ependymitis.

ACKNOWLEDGEMENT: This case is one of a series now being prepared for publication by Drs. J. C. Harvey and J. N. DeKlerk who have kindly permitted its publication here.

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It is well known that both strong coffee and tea will often prevent a threatened megrim seizure, especially under the milder form of "nervous headache," and sometimes they will quicken the departure of a fully-developed attack. Like all remedies of the same class, they are uncertain in their effects, acting admirably with some persons on some occasions and entirely failing with others. They should be given strong without sugar or milk, and, if possible, on an empty stomach; and they are more effectual when the patient is accustomed to use them sparingly as articles of diet. Both Tissot and Lebert recognize this curative power of coffee in megrim, and Dr. Symonds observes: "I am not acquainted with any agents which equal these substances in the power of removing headache without leaving inconvenient results. And as their physiological action is so purely cerebral, restoring the intellectual faculties, and ministering to the sensations of personal well-being, as well as lessening any sad emotions, we have here an adequate presumption, were any required, that this headache is seated in the nerves, which are immediately related with the molecular action of the brain."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders*, published in 1873.

CASE REPORT

Cerebrospinal Rhinorrhea with Pituitary Tumors

Luigia Norsa, M.D.

SINCE the first description of cerebrospinal rhinorrhea by Willis in 1676,[1] the condition has been reported following trauma (both accidental and surgical), infections of the nose and of the paranasal sinuses, congenital anomalies, and brain tumors.

The term "spontaneous, primary, or idiopathic" rhinorrhea was at first applied to all but the posttraumatic cases,[2] but more recently[3] it has been restricted to instances where osseous defects, chiefly in the region of the cribriform plate and presumably of congenital origin, were demonstrable at surgery or at postmortem examination.

The escape of cerebrospinal fluid from the nose represents numerically only a medical curiosity. Nevertheless, this condition constitutes a challenging therapeutic problem from both medical and surgical standpoints, since once a pathway has become established between the subarachnoid space and the outside world, the danger of meningitis, as well as of spontaneous pneumocephalus, is forever present. The etiologic agents have included the pneumococcus, staphylococcus, non-hemolytic streptococcus, and hemophilus, which gained access to the cranial cavity whenever the intracranial pressure had shifted in the direction of greater negativity (coughing, sneezing, nose-blowing).

CASE REPORT

A 29 year old white man was first admitted to the Bronx Veterans Administration Hospital on December 4, 1950 in a state of stupor and restlessness. Two weeks before he had developed an upper respiratory infection with transient frontal and occipital headaches, which had recurred 12 hours prior to admission in association with fever and vomiting. The patient's present illness dated back to puberty when he became obese and secondary sex characteristics failed to develop. In 1941, at age 20, he was noted to have a "Fröhlich habitus," and shortly thereafter developed severe bifrontal headaches. In 1943 skull films revealed an enlarged sella turcica. A diagnosis of chromophobe adenoma was made at Walter Reed Hospital. The headaches responded to radiotherapy. In 1947 the patient noted the development of intermittent profuse watery discharge from both nostrils, intensified by tilting the head forward. In June 1948 he was treated for pneumococcus type XVIII meningitis at another institution. There was no history of head trauma or of intracranial and nasal surgery.

Physical examination on December 4,

From the department of neurology, Veterans Administration Hospital, Bronx, New York.

1950 revealed a markedly obese, acutely ill, disoriented male with scant body hair who appeared younger than his stated age. Fever was 105° F. Pupils were dilated, reactive and equal; the neck was stiff, and bilateral Kernig signs were found. Deep tendon reflexes were hypoactive but equal. The clinical impression of meningitis was confirmed by lumbar puncture, which revealed elevated pressure and 10,000 white blood cells per cu. mm., predominantly polymorphonuclear leukocytes; spinal fluid was negative on smear and later on culture.

Following administration of penicillin, sulfadiazine, and streptomycin, his temperature fell to normal by the fourth day. The rhinorrhea resumed, ranging in volume from 3 to 20 cc. per day, and the nasal secretion proved to be spinal fluid by virtue of its sugar content of 70 mg. per cent.

Otolaryngologic consultation was noncontributory, but skull films revealed a marked enlargement of the sella turcica with erosion of the clinoid processes and suggestion of a break into the roof of the sphenoid sinus (figure 1). Laboratory investigation of pituitary functions failed to disclose any abnormalities. Visual acuity was 20/20 bilaterally, and fields were intact. Skull films, acuity, and visual fields showed no change during the following ten months.

The patient was discharged in February 1951. He was supplied with oral penicillin to be taken at the earliest sign of a respiratory infection, and instructed to report to the hospital at once for additional therapy. He thus weathered successfully several colds until June 1951, when he was readmitted with a temperature of 100.8° F. only because of headaches resembling in type those experienced with his last episode of meningitis. Spinal fluid on readmission showed elevated pressure, 820 white blood cells per cu. mm. (95 per cent polymorphonuclear cells), low sugar, and again negative smear and culture.

FIG. 1. Skull film of reported case. Note enlarged sella turcica.

Notwithstanding prompt institution of penicillin and sulfadiazine, the rhinorrhea stopped during the first five hours, the neck became stiff, and the temperature rose to 106° F. Clinical improvement followed in the next 24 hours.

The question of future management was considered at length by both the neurologic and neurosurgical services. In view of the multiple episodes of meningitis recurring at diminishing intervals of time it was finally concluded that surgery aimed at the repair of the cerebrospinal fluid leak was justified. In October 1951 a frontal craniotomy was carried out. Inspection over the cribriform plate failed to reveal any unusual dural openings. After elevating the brain, a bluish mass was seen occupying the sella turcica anterior to the chiasma. Sudden massive escape of venous blood precluded further exploration and identification of any defects.

The immediate postoperative course was uneventful, the patient being coherent and able to move all extremities. On the second postoperative day, however, he went into coma and expired quietly a few hours later.

At autopsy, the sella was found to be markedly enlarged and ballooned. Its lateral wall and clinoid processes on the left side were eroded by hemorrhagic tumor tissue which extended about, but did not invade, the internal carotid artery and the cavernous sinus. The floor of the sella was markedly atrophic and at one point opened into the sphenoid sinus. The remainder of the brain showed changes compatible with operative trauma and edema; there was no evidence of hydrocephalus.

The pathologic report was chromophobe adenoma. The microscopic pattern consisted of cords and columns of cells of variable size, separated by pale eosinophilic material (figure 2). Tumor cells were seen infiltrating the leptomeninges of the optic chiasma (figure 3) and of the hypothalamus. In view of the cell variability and of the lepto-

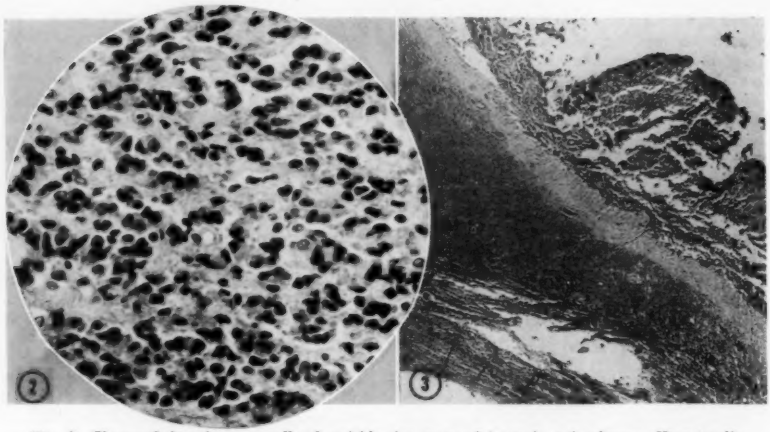

FIG. 2. Chromophobe adenoma: cells of variable size arranged in cords and columns. Hematoxylin and eosin stain. FIG. 3. Chromophobe adenoma infiltrating the optic chiasma. Hematoxylin and eosin stain.

meningeal invasion, the question of pituitary malignancy arises.

The presence of tumor cells in the leptomeninges suggests a possible explanation for the leakage of spinal fluid in this case. The sequence of events is illustrated in schematic fashion in figure 4. The pituitary is seen lodging in the sella turcica, its capsule being intimately adherent to the bone. The subarachnoid space forms a collar about the stalk, but does not proceed distal to it. In its growth the adenoma, after breaking through its capsule, expanded inferiorly causing erosion into the sphenoid sinus, as well as superiorly through the diaphragm, and thence by direct extension into the subarachnoid space. Thus the latter came into communication with the sphenoid sinus, without the sinus being necessarily invaded by tumor tissue. From the sinus, the spinal fluid may have reached the nose through the ostium and the spheno-ethmoidal recess.

REVIEW OF THE LITERATURE

A variety of slow growing supratentorial[4,5] and infratentorial[2,6] neoplasms, including osteomas,[7,8] meningiomas,[9,10] pinealomas,[11] and angle tumors,[12] have presented themselves preoperatively in association with cerebrospinal rhinorrhea; a total of 12 such pathologically verified tumors is on record. Erosion of dura and of bone either directly or indirectly following increased intracranial pressure of long standing appears to be the common denominator in this group, which has

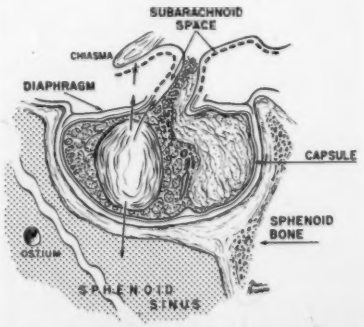

FIG. 4. Anatomic relationships of the pituitary gland. Note erosion of tumor through the sellar floor and extension into the subarachnoid space.

been adequately discussed in previous reviews.[13,14]

The association of pituitary tumors with cerebrospinal rhinorrhea was commented upon in Cushing's days only in connection with its rare postoperative occurrence; one such case operated on in 1928 was later reported by Shea.[15]

Although neither erosion through the basisphenoid into the nasopharynx (the commonest way of extension for the chromophobe adenomas[16]) nor infrasellar penetration into the sphenoid sinus invariably lead to clinical rhinorrhea, it has been possible to collect from the literature a number of cases in which the condition was present preoperatively.

Baxter's patient[17] has been referred to in the past as such an example. Although the symptomatology is strongly suggestive of pituitary tumor, the failure of a cursorily performed autopsy to demonstrate such a neoplasm detracts from the validity of the case. In 1895 Gutsche[18] reported briefly on a 34 year old male with rhinorrhea who, following death from meningitis, showed a pituitary tumor at autopsy. Unfortunately more detailed description of it is not available.

Boyd in 1910[19] described a 36 year old man with bitemporal hemianopsia progressing to blindness who also died of meningitis. Autopsy showed a markedly enlarged sella, opening into the maxillary antrum, separated from the nasopharynx by a membranous partition, and housing "a soft friable vascular tumor" extending superiorly to the infundibulum. His microscopic description strongly suggests that he was dealing with a chromophobe adenoma.

Matzdorff's patient[20] was a 48 year old female who died of meningitis shortly after the onset of rhinorrhea. Postmortem examination revealed a cyst, hazelnut in size, encompassing the pituitary stalk and compressing the gland. The reason for the rhinorrhea was not clear.

In 1932 Friedmann[21] reported a 30 year old female with a ten year history of headaches, progressive visual impairment, and hypothalamic symptoms. At autopsy a tumor involving the hypophysis and hypothalamus was found, and termed microscopically a "gliome cellulaire sarcomateaux malin typique." Again the occurrence of the rhinorrhea could not be accounted for.

Som and Kramer's case[14] succumbed to hemophilus meningitis three years following the onset of rhinorrhea. This was a 44 year old woman with a history of headaches and x-ray evidence of depression of the floor of the sella. No other neurologic details were given. Postmortem examination revealed "a large pituitary neoplasm." Serial sections of the paranasal sinuses showed the presence of a fistulous tract leading from the dura through the cribriform plate into a defect of the olfactory mucosa.

The only other verified case of pituitary tumor with rhinorrhea on record is that of a 42 year old woman who developed headaches and impaired vision in 1931, followed by rhinorrhea in 1949. A subsequent nasal biopsy confirmed the extension of her chromophobe adenoma into the nasal cavity.[22]

Mention of several other pituitary tumors with preoperative rhinorrhea is to be found in the literature,[7,9,23,24] but all these cases, which include two possible craniopharyngiomas, remain unverified. The rhinorrhea in one additional suspected Rathke's pouch tumor was found on craniotomy to be secondary to congenital bony defects in the cribriform plate.[25]

In conclusion, a search for brain tumors in association with preoperative rhinorrhea reveals six proven pituitary neoplasms, including our own case, one pituitary cyst, and 12 additional miscellaneous supratentorial and infratentorial tumors.

We may therefore conclude that, although a rare feature of pituitary neoplasms, cerebrospinal rhinorrhea seems to be more frequently associated with them than with any other type of brain tumor. A single explanation cannot account for this. The rhinorrhea may be related fortuitously to coexisting defects about the cribriform plate. At times, direct pressure exerted upon the underlying bone leads to erosion of the base of the skull with extension into the paranasal sinuses and into the nasopharynx, although such an extension does not necessarily result in clinical rhinorrhea. The case presented here suggests that pressure necrosis of the sella turcica, coupled with invasion of the subarachnoid space by tumor cells, may in some instances account for rhinorrhea.

SUMMARY

1. A case of cerebrospinal rhinorrhea with three recurrences of meningitis is presented. At autopsy, a chromophobe adenoma eroding the sella turcica and infiltrating the leptomeninges was found.

2. Rhinorrhea with pituitary tumors is uncommon, but it occurs more frequently in association with them than with any other type of brain tumors.

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Neurology BOOK REVIEWS

The 1952 Year Book of Neurology, Psychiatry and Neurosurgery.

Edited by Roland P. Mackay, M.D., Nolan D. C. Lewis, M.D. and Percival Bailey, M.D. 1953. Chicago: The Year Book Publishers, Inc. 603 pages. $6.00.

As in years past, this annual volume sums up the significant contributions in the related fields of neurology, psychiatry, and neurosurgery. Dr. Mackay, as editor of the section on neurology, uses his customary discrimination in choice of articles reviewed, and adds many sage editorial comments. His introductory review is an excellent summary of the year's work. Dr. Lewis lists as the four main areas of development in psychiatry during the past year the trends in psychosurgery, psychosomatic medicine, pharmacologic investigations, and psychodynamics. Because of the ever-increasing amount of psychoanalytic literature and the difficulty in abstracting it, only current reviews in this field are listed. The readers of the *Year Book* will welcome the return of Dr. Bailey as editor of the section on neurosurgery. His comprehensive introduction with historical references is stimulating reading, and his carefully abstracted reviews, editorial comments, and suggestions add to the value of the volume.

It is most difficult, even for the most assiduous reader, to keep abreast of the increasing literature in neurology and related fields. However, with the aid of editors such as those chosen for this *Year Book*, one may review the most significant contributions and timely advances.

R. N. DE J.

Estudios De Neurologia Clinica

L. Barraquer-Ferré, M.D. (With a preface by Robert Bing.) 1952. Barcelona, Spain: José Janés. 755 pages. $10.00.

This volume embodies Spain's contributions to international neurology. The author is director of the School of Neurology at the Santa Cruz and San Pablo Hospital in Barcelona, honorary president of the Neurological Association of Spain, and holds honorary memberships in numerous neurological societies, including those in Paris and the United States. In 1952 the Brazilian journal *Arquivos de Neuro-Psiquiatria*, published a Festschrift in honor of his sixty-fifth birthday.

The emphasis in this book is on the author's own observations. He states that positive Babinski, toe-spreading and grasp reflexes in children 12 to 18 months of age have pathognomonic significance. A positive Babinski reflex should lead one to suspect a lesion involving cortical area 4 of Brodmann; toe-spreading suggests the presence of

such disorders as congenital hydrocephalus, cerebral asphyxia or hemorrhage due to dystocic disturbances during delivery, and diffuse and spreading lesions of the premotor cortex; and the grasp reflex, most readily elicited by stroking the first intermetacarpal space, indicates a lesion of the superior part of area 6a.

From animal studies, the author has concluded that the normal functioning of the vestibular system depends primarily on neural impulses emanating from the parapyramidal area (of Bucy) of the frontal lobe.

In glossopharyngeal neuralgia, in which paroxysmal pain radiating to the ipsilateral occiput and parietal areas can be elicited by exerting pressure on the region one or two centimeters beneath the occipital border of the mastoid process, he advocates division of the intracranial portion of the glossopharyngeal nerve, according to the method of Dandy. (A view of the operative field through a craniotomy exposure is illustrated.) In neuralgia involving the auricular branch of the vagus nerve (nerve of Arnold), he advocates dividing roots C-1, C-2, and C-3. In a case of polyneuritis due to D.D.T. inhalation, spontaneous recovery occurred in several months.

Two cases of amyotrophic lateral sclerosis are cited in which the disease was transmitted as a dominant character. Thirteen cases of syringomyelia occurring in one family are described; here, too, the disease was transmitted as a dominant character. Reference is made to ten cases of Barraquer's disease (generalized progressive lipodystrophy), in one of which the disorder occurred in members of three generations. From the nature of the metabolic disturbances (hyperfolliculinism, hyperthyroidism and faulty fat metabolism) in one of these cases, the author felt it likely that degenerative changes existed in the hypothalamus, and that a hyperactivity of the spinal sympathetic system had resulted. The nine cases of the "sympathetic form" of lipodystrophy were ascribable variously to neurogenic, hormonal and metabolic factors and to encephalitic disease. In the section dealing with tumors, the author illustrates and describes in some detail a racemose colloid-containing cyst in the lateral ventricle, causing ventricular obstruction.

The author describes three cases of a new clinical entity in which the onset was characterized by suddenly developing severe pain in the lower extremities. The two men and one woman concerned were 34 to 43 years old. Gangrene occurred six to eight days after the onset. Sympathectomy was unavailing, so that amputation of both legs was necessary in all three cases.

Dr. Barraquer-Ferré has perfected the art of describing diseases in general terms and providing specific examples. The illustrations, which number 225, are excellent and many of them are self-explanatory to the reader not versed in Spanish. Much space (104 pages) is given over to the neurologic examination. The fact that the description of the neuralgias and neuritides covers 135 pages means that the author has the practitioner in mind as he writes. Treatment of many neurologic disorders is fully covered. The many references represent a composite of world literature, emphasizing those in Spanish.

This is a highly important treatise from a clinical standpoint, as it brings to the fore the great amount of information which may be obtained without recourse to ventriculography, encephalography, myelography, arteriography and electroencephalography. Robert Bing, who wrote the preface to this book, stated that it provides a "perfect knowledge of neuroanatomy, neurophysiology and clinical neurology" and brings out those subtleties which mark a masterpiece.

L. M. C. & W. H.

Neurology

Revascularization of the Brain in Mental Defectives

George A. Jervis, M. D., Ferdinand F. McAllister, M.D., Bruce M. Hogg, M.D., and Ralph A. Deterling, Jr., M.D.

In 1949, Beck, McKhann, and Belnap[1] introduced a new operative procedure designed to increase the arterial blood supply to the cerebral cortex by establishing an arteriovenous anastomosis between the carotid artery and the internal jugular vein. The increased blood supply, in the opinion of Beck and coworkers, results in a better oxygenation and, consequently, in increased nourishment of cortical cells. It was claimed that the operative procedure produces beneficial effects in patients in whom the function of cortical cells has been rendered abnormal but not entirely suppressed through past injury.

The operation has been performed on several hundred mentally defective patients and, occasionally, on patients affected with senile dementia, arteriosclerotic psychosis, and sequelae of brain embolism. Results have been published, however, in a few more than 300 patients. Since a wide discrepancy of opinion exists concerning the value of the procedure, it was considered of some interest to report briefly the following series of 25 patients.

METHOD AND MATERIALS

The surgical procedure was carried out using the technic described by Beck and coworkers.[1,2] In all patients but one, a side-to-side anastomosis was

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made between the external carotid and the internal jugular, the opening averaging about 4 mm. in diameter. In only one patient was the anastomosis made between the common carotid and the internal jugular, since the carotid bifurcation was abnormally high. The operation was performed in every case on the right side, and the jugular vein was tied and cut below the fistula.

Every patient was submitted to a series of preoperative examinations which included clinical and neurologic examinations, x-ray of the heart for determination of size, air encephalogram, electroencephalogram, and psychometric examination. Postoperatively, the intelligence quotient was determined at intervals of one, three, six, and 12 months, using alternatively the L and M form of the revised Stanford-Binet test. The electroencephalogram was repeated at least twice, at one month and at six to 12 months. Neurologic examination was repeated at various intervals and all patients remained under observation in the hospital from two and one-half to three years after operation.

The operative procedure was used for 25 children who varied in age from three to 20 years and in intelligence quotient from 10 to 70. The first group (cases 1 to 10) consisted of ten postencephalitic mental defectives. The children had developed normally both physically and mentally until the acute encephalitic episode. Only one showed evidence of motor impairment. None had shown progressive neurologic symptoms or mental deterioration. Air encephalograms were negative in all and only three showed minor electroencephalographic abnormalities. The encephalitis was of bacterial origin (pneumococcus) in one case and presumably viral in all the other cases, although no virus had been identified. From all available evidence, these patients were considered suitable for revascularization, since presumably damage from the encephalitic process was not sufficiently extensive or severe to cause clinical manifestations apart from mental deficiency.

The second group (cases 11 to 17) consisted of seven posttraumatic mental defectives. These patients had a clear-cut history of traumatic birth and showed evidence of brain injury during the neonatal period. On neurologic examination, three patients had hemiparesis and four exhibited mild generalized muscular hypertonicity. Air encephalogram showed evidence of cortical atrophy in one patient but was essentially negative in the other six.

The third group (cases 18 to 24) consisted of seven epileptic patients. All were mentally defective. Air encephalograms were normal. On electroencephalogram, all had diffuse abnormalities with no evidence of focus. History was noncontributory and neurologic examination essentially negative. Response of all patients to usual antiepileptic drugs was poor.

Finally, a patient affected with infantile schizophrenia, who showed an apparent intelligence quotient of 40, was included in the series (case 25).

RESULTS

The effect of the operation on the intelligence quotient of patients is seen in table 1. If one assumes that a change of less than ten points is not significant, it may be seen that in no case was there an appreciable change which

TABLE 1

EFFECT OF REVASCULARIZATION OPERATION ON INTELLIGENCE QUOTIENT, EEG, AND SEIZURES

Case No.	Age	Intelligence Quotient				EEG	Seizures	Complications
		Pre-	Postoperative					
			1 mo.	6 mo.	1 yr.+			
1	17	34	32	33	33	No change	No change	None	Closure
2	12	8	9	11	9	No change	No change	None	None
3	12	29	25	25	23	No change	Worse	None	Proptosis-exophthalmos
4	12	32	27	30	31	No change	No change	None	Proptosis-exophthalmos
5	9	13	14	–	14	No change	No change	None	Proptosis (slight)
6	8	72	71	72	70	No change	Worse	None	Venous ectasia
7	7	44	44	–	44	No change	No change	None	Proptosis-exophthalmos
8	14	20	21	18	20	No change	No change	None	Closure
9	9	14	12	13	12	No change	No change	None	None
10	8	12	12	13	12	No change	No change	None	Proptosis-exophthalmos
11	5	23	9	9	10	Worse	No change	No change	Closure
12	15	51	51	46	45	No change	No change	None	Closure
13	12	26	24	26	33	No change	No change	None	Closure
14	15	39	38	34	38	No change	No change	No change	None
15	12	42	49	41	48	No change	Worse	Worse	Exophthalmos
16	12	13	–	12	12	No change	No change	None	Proptosis
17	3	35	35	36	36	No change	No change	None	Venous ectasia
18	8	26	26	25	–	No change	Worse	Worse	Died in status
19	20	17	18	17	–	No change	Better	Better	None
20	8	48	59	58	49	Better	No change	Better	None
21	10	23	24	–	24	No change	No change	Worse	Closure
22	12	28	32	28	30	No change	No change	No change	Exophthalmos
23	4	45	40	42	26	Worse	Better	Better	Closure
24	9	43	40	42	43	No change	No change	No change	Closure
25	8	40	35	41	33	No change	No change	None	Proptosis-exophthalmos

could be attributed directly to the operation. One patient (case 20), an epileptic with erratic behavior, gained 11 points. This gain might be attributed to temporary variations in attention span. Another epileptic (case 23) lost some 20 points and showed, in addition, deterioration of the behavior pattern; this patient was probably suffering from a progressive type of encephalopathy.

Epileptic seizures improved in three patients as far as frequency and severity of attacks were concerned. However, the improvement was temporary and some six months after the operation no change was noticeable. One (case 23) showed more severe attacks. Two patients (cases 15 and 21) became worse shortly after the operation, and one (case 18) died in status epilepticus six months after the operation.

Electroencephalograms showed some improvement in four cases: in two very slow diffuse patterns (S_3 in Gibb's classification) became less slow (S_2); in two others, less disorganization was temporarily present immediately after

the operation. In four patients, the record was considered worse. In all other cases no significant changes were noted.

General behavior. Some improvement was noted in four patients immediately after operation. Three patients were more docile and more cooperative, and one child who had been moody and "cranky" showed a better disposition and more cheerfulness. It should be noted, however, that because of various tests, the operative procedure, and close observation, the patients were necessarily exposed to constant individual attention and care to which they were not accustomed in the institutional set-up. Improvement of behavior could be explained by this changed attitude of the personnel toward the children. Information from visiting parents and relatives was not taken into account in assessing improvement of general behavior.

In no patient was the neurologic picture modified by the operation.

In eight patients, *angiographic study* of the anastomosis was performed by injecting contrast medium (Diodrast) into the common carotid artery at various intervals after the operation. In almost all cases a fairly clear-cut picture of the anastomosis was obtained and the contrast medium was seen to fill the internal jugular vein and the transverse sinus of the right side. In four patients, the transverse sinus of the left side and the left internal jugular vein were visualized (figure 1). In two patients, the venous plexus of the right mastoid region appeared filled with Diodrast. At no time did the longitudinal sinus contain contrast medium.

Complications. Immediate complications after the operation were not observed. Elevated spinal fluid pressure was noted in most patients immediately after establishing the anastomosis and for several days thereafter. Vomiting and slow pulse were observed only in two patients and repeated withdrawal of fluid resulted in prompt relief of the symptoms. No choked disk was noted. Only four patients complained of headache; because of the low mental age of many subjects, this symptom could not be properly evaluated.

The most common complications were proptosis of the right eye with exophthalmos accompanied frequently by hyperemia and occasionally by hemorrhages of the conjunctiva. In one patient (case 3) retinal hemorrhage was observed. Exophthalmos and slight proptosis persisted for over two years in nine cases (36 per cent). This condition was often accompanied by puffiness of the eyelid and periorbital region and some tortuosity of the veins of the temporal region. In nine cases, dilatation of the jugular vein immediately above the anastomosis was observed. In one patient this dilatation was painful and resulted in stiffness of the neck. Only one patient complained of annoying "buzzing" in the right ear. Enlargement of the heart was not noted.

Closure of the fistula occurred spontaneously in eight patients (32 per cent) between six months and two years after operation. If these cases are excluded in assessing the incidence of complication, the percentage is raised to 70, only five patients being free of complications at the third year. However, only in three patients were the complications so severe as to require

FIG. 1. Right carotid angiogram showing filling of the dilated right internal jugular vein and right lateral sinus. The left lateral sinus, left jugular vein, and some extracranial veins contain considerable amounts of contrast medium.

prompt repair of the fistula. All abnormal signs and symptoms disappeared promptly upon closure of the fistula.

COMMENT

Results on the effects of Beck-McKhann's procedure have been reported in a total of 331 cases. McKhann and coworkers[2] reported 120 cases; Tarlov and coworkers,[3] three cases; 33 patients were described by Kessler;[4] 33 by Hammer and coworkers;[5] five by Gurdjian and coworkers;[6] 65 by Stowell and Hayne;[7] in Norway, Selley and coworkers[8] reported on 14 patients; in France, Klein and coworkers[9] on 53 cases; and in Sweden, Torkildsen and Koppang[10] on five cases.

As seen in table 2, the results of the operation thus far reported in the medical literature differ considerably. While the majority of investigators describing small series of cases report no significant improvement, considerable success is claimed by few others whose series of cases are much larger. In the attempt to clarify such wide discrepancies, one may note, first of all, that the criteria for selecting suitable candidates for operation are not sufficiently precise to assure uniformity of samples. Thus, the series of cases reported by McKhann and coworkers[2] and by Klein and coworkers[9] may have included a

TABLE 2

RESULTS OF REVASCULARIZATION OPERATION REPORTED IN THE LITERATURE

Author	I.Q.			EEG			Epilepsy			Cerebral Palsy		
	No change	Better	Worse	No change	Better	Worse	No change	Better	Worse	No change	Better	Worse
McKhann[2]	41	32*	0	–	–	–	28	22	0	13	16	0
Tarlov et al.[3]	3	0	0	–	–	–	–	–	–	–	–	–
Kessler[4]	31	1	1	–	–	–	4	2	–	–	–	–
Hammer[5]	10	1	0	–	–	–	–	–	–	10	1	–
Gurdjian[6]	4	1	0	2	2	–	2	1	0	0	1	0
Stowell[7]	61	4	0	10	6	9	17	8	–	–	–	–
Selley[8]	14	0	0	7	3	2	4	2	0	–	–	–
Klein[9]	20	25	0	–	–	–	1	11	–	–	–	–
Torkildsen[10]	–	–	–	–	–	–	2	1	2	–	–	–
Present series	22	1	2	18	4	4	4	3	2	7	0	0
Total	206	65	3	37	15	15	62	50	4	30	18	0
Percentages	75	24	1	56	22	22	53	43	4	62	38	0

*Including 16 "subjective" improvement.

larger number of patients with mild brain damage than other groups in which the results were negative. In the present series only, half of the patients had an intelligence quotient below 30, suggesting considerable damage to the brain.

In assessing the improvement in intelligence quotient, changes of a few points may have been considered significant by some, insignificant by others. Since in several published reports no actual figures are given, no definite conclusion on this point can be reached. In the present series, changes of less than ten points on the Binet scale were not taken into account.

Evaluation of improvement in frequency and severity of epileptic attacks and appraisal of the electroencephalographic pattern may vary from one observer to another depending upon length of observation. The most striking results obtained by some investigators after revascularization were noted during a relatively short period and might have been transitory in character. In fact, transitory improvements are not infrequently observed after air encephalograms and general anesthesia. Moreover, in very young subjects, improvement of electroencephalographic tracings might be the result of maturation of cortical patterns. It may be noted that some investigators have relied on so-called subjective signs in their evaluation of improvement; such terms as "increased brightness," "alertness," "greater attention," and "less instability" occur frequently and the information on these items of general behavior was usually obtained from parents and relatives of patients, a source of information which is apt to be misleading when the unfortunate parent expects much from the operative procedure.

Perhaps a more fundamental reason is at the basis of the numerous failures. The procedure is based on the assumption that arterial blood will reach

the cerebral cortex by way of the jugular vein, the transverse and the sagittal sinus, and its tributary veins. The evidence brought forward[1,2] consists of experiments in dogs showing filling of cortical bed with India inks and radioactive iodine after injection of these substances in the jugular vein under arterial pressure. However, other data apparently disprove this basic assumption. In the present series, angiographic evidence was obtained showing that the arterial blood which flows into the right internal jugular vein by-passes the cerebral circulation and shunts to the left jugular vein through the transverse sinuses. No filling of the sagittal sinus occurred.

Similar results were first presented by Tarlov and coworkers[3] who, in addition, found that the amount of blood entering the right cerebral hemisphere appeared to be decreased since most of the blood shunted across the jugular veins and transverse sinuses. The findings were confirmed by Gurdjian and coworkers[6,11] and Selley and coworkers.[8] In the latter series of cases the anastomosis was end to end and, consequently, more apt to fill the venous channels. In addition, measurement of the oxygen content of the sagittal sinus immediately after establishment of the fistula showed either no change from preoperative levels[6,11] or often actual reduction.[8] The reduction of oxygen content can be interpreted as evidence of venous stasis in the longitudinal sinus. Additional indirect evidence in favor of a lack of increased vascularization was obtained by pathologic examination of four patients who were operated upon elsewhere and who died from intercurrent causes two to three years after operation. The cortical veins were normal although arterialization of the walls should have become apparent, if the veins had carried arterial blood.[12]

Apparently, the presence of venous shunts defeats the purpose of the operation. On the other hand, it would seem doubtful that even in the absence of venous shunts increased vascularization of the brain could be obtained. In fact, when the fistula was large and a considerable amount of blood flowed through, the main result was impairment of venous drainage with consequent increase of cerebrospinal fluid, presumably followed by decrease of blood flow through the brain[13] and increase of cerebrovascular resistance.[14]

Although complications in this series of cases were not serious, the rationale of the procedure was based on too incomplete data, and the results were not sufficiently encouraging to justify further trials.

SUMMARY

The operative procedure of Beck, McKhann, and Belnap aimed at revascularization of the brain was carried out on 25 mentally defective children. In ten children, the mental defect was postencephalitic, in seven, posttraumatic in origin; seven children were epileptic defectives; and one suffered from childhood schizophrenia. The period of postoperative observation extended to two years or more.

No significant improvement was observed in intelligence quotients, clinical symptomatology, and electroencephalographic findings. Data obtained

by other investigators are summarized and some theoretical aspects of the operative procedures are briefly discussed.

The assistance of Dr. Miguel Ramos in performing the arteriograms is gratefully acknowledged.

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Again, the phenomena of megrim are almost exclusively sensory, and if spasmodic or convulsive movements occur, they are quite exceptional and secondary to the sensorial disturbance; as for instance the vomiting which sometimes follows a high degree of nausea, and the facial spasm which has been known to attend the pain. Hence we infer that the disorder is limited for the most part to the sensory tract and the ganglia of the sensory nerves, from the optic thalamus above to the nucleus of the vagus below. And since in the typical seizure the visual disorder is always the initial symptom, the headache the middle, and the nausea and vomiting last, we infer that the "storm" has its point of departure or principal focus in the optic thalamus, and that its normal course is from above downwards, or from before backwards, in the sensory tract.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Results of Transorbital Lobotomy in 400 State Hospital Patients

William W. Wilson, M.D., A. R. Pittman, M.D., R. E. Bennett, M.D., and R. S. Garber, M.D.

In a previous report[1] the results of transorbital lobotomy in 200 state hospital patients were presented. It is the purpose of this paper to review findings in 400 patients, and in particular to emphasize the further changes that have taken place in the original 200. A project to study the results of transorbital lobotomy was begun in January 1950, although one operation had been performed late in 1949. As is customary with operations of this type, the patients selected had failed to improve on all other types of psychiatric therapy and were considered hopeless. Most of them had been in seclusion for many years and were the most difficult care problems in the hospital.

In 1951, when compiling statistics for the original 200 cases, it became quite evident that excellent progress had been made both in the therapy of long-term patients and in the economic problem presented by the chronically psychotic. It is felt that figures presented here will justify continuation of this type of operation. In the past year it was planned that the operation be given to some patients whose duration of illness was shorter than most of those of the original 200, but in general the types of cases have remained similar although several severe psychoneurotic patients were included. Fortunately there have been relatively few nonoperative deaths, the causes of which have been cancer, pneumonia, tuberculosis, cystitis, and other intercurrent infections. Eight such cases dying less than one year postoperatively have not been included in the statistics due to the brevity of postoperative observation.

Classification of results has been similar to that of the previous report. Following interviews by several of the authors and reports from the ward nurses, the cases have been placed in one of five groups: out of the hospital, good improvement, fair improvement, no improvement, and operative death. The first and last groups are easily classified, although it should be stated that a small number of those leaving the hospital have returned to other state institutions. These have usually been epileptic or mentally deficient patients who in effect are able to return to their home environment. Extremely strict criteria have been employed in consideration of the good, fair, and unimproved

From the New Jersey State Hospital, Trenton.

TABLE 1
DISTRIBUTION BY SEX AND COLOR

Number of cases	400*
Male	200
Female	200
White	340
Negro	60

*8 nonoperative deaths not included.

TABLE 2
RESULTS

	Number	*Per cent*
Out of hospital	79	19.75
Good	114	28.50
Fair	95	23.75
Unimproved	104	26.00
Operative death	8	2.00
Total	400	100.00

groups, and if any doubt arose the patient was put in a lower group. It should be stated here that evaluation is based on preoperative condition and not on a hypothetical cure.

The operation itself has been described by Freeman,[2,3] and the technic need not be further amplified here except to state that all operations were bilateral. We consider the operation a minor one, and as such it does not require a formal operating room. Several ward dressing rooms were used and the ward personnel have been trained to assist.

Table 1 shows the general distribution of cases as to sex and race. The figures generally are in accord with the hospital population. The criteria for the selection of cases did not include sex or race, but those patients were

TABLE 3
DISTRIBUTION BY DIAGNOSIS

	Number	*Average age*	*Average duration of illness (years)*
Schizophrenia	267	37.6	11.2
Manic-depressive psychosis	20	48.6	11.8
Involutional psychosis	12	57.3	7.0
Psychopathic personality	17	31.4	8.8
Psychosis with mental deficiency	48	31.6	11.7
Psychosis with epilepsy	20	32.6	9.5
Miscellaneous organic psychosis	13	53.4	8.6
Psychoneurosis	3	55.0	8.0
Total	400	37.7	10.8

TABLE 4
TYPES OF SCHIZOPHRENIA

	Number	Average age	Average duration of illness (years)
Simple	22	38.9	14.4
Hebephrenic	79	33.5	10.1
Catatonic	66	35.0	11.0
Paranoid	100	42.3	11.4
Total	267	37.6	11.2

TABLE 5
RESULTS BY DIAGNOSIS

	Out of hospital	Good	Fair	Unimproved	Operative death
Schizophrenia	47	84	62	69	5
Manic-depressive psychosis	3	10	4	3	–
Involutional psychosis	4	2	3	2	1
Psychopathic personality	6	–	6	5	–
Psychosis with mental deficiency	13	10	10	14	1
Psychosis with epilepsy	–	5	7	7	1
Miscellaneous organic psychosis	4	3	3	3	–
Psychoneurosis	2	–	–	1	–
Total	79	114	95	104	8

TABLE 6
RESULTS IN SCHIZOPHRENIA

	Out of hospital	Good	Fair	Unimproved	Operative death
Simple	–	9	5	8	–
Hebephrenic	16	17	14	32	–
Catatonic	14	21	19	11	1
Paranoid	17	37	24	18	4
Total	47	84	62	69	5

TABLE 7
RESULTS ACCORDING TO SEX

	Out of hospital	Good	Fair	Unimproved	Operative death	Total
Male	31	53	58	54	4	200
Female	48	61	37	50	4	200

TABLE 8
RESULTS OF CASES RECEIVING SECOND OPERATIONS

	Number	*Out of hospital*	*Good*	*Fair*	*Unimproved*	*Operative death*
Two operations	24	2	4	10	8	–
Operation following prefrontal lobotomy	7	–	3	2	2	–

chosen who had failed to respond to other types of therapy, were chronically ill, and whose families would grant permission for the operation. The controls consisted of other hospitalized cases of the same type whose families would not consent to operation or who could not be operated upon for other reasons.

Table 2 shows the overall results, with about one-half of the cases benefited greatly and another 25 per cent somewhat improved.

Table 3 shows the distribution by diagnosis and the average age and duration of illness at the time of lobotomy. Table 4 further classifies the diagnosis of schizophrenia.

Table 5 shows the results by diagnosis and table 6 the results according to type of schizophrenia.

Table 7 indicates the results according to sex. It will be seen that the female patients responded better than the males. This is a reversal of the results reported in the original 200 cases. Comparison will be shown below.

It has been our practice to observe these patients for the first three postoperative months without using any form of shock therapy. Patients are urged to take part whenever possible in occupational therapy and other activities of the wards and grounds of the hospital that had been denied them preoperatively due to their disturbed state. If satisfactory improvement is not attained within three months, it is customary to institute a course of electroshock therapy. If still no progress has been made in another three months, the unimproved patients are scheduled for a second transorbital lobotomy. In this second operation, cuts are made at depths of 4 and 6 cm. as well as at 5 and 7 cm. from the lid. It will be seen from the number of cases having received two operations (table 8) that not all of the unimproved cases have as yet been reoperated upon. Results in those who had been operated on by the prefrontal route prior to transorbital lobotomy are also listed.

Second operations have been performed at intervals of several months to several years after the initial operation. It is evident that even though the first operation fails, there is still a chance of improvement with a second operation. As a matter of fact, one of the most successful cases required two operations before satisfactory improvement could be maintained. An abstract of the case history follows:

A 50 year old chronic paranoid schizophrenic had been in continuous residence in the state hospital for 22 years. He was domineering and threatening, and adjusted very poorly on all wards. He was very clever in scheming to set one attendant against another and to upset ward routine. He became sexually dangerous to certain members of the staff and

TABLE 9
COMPARISON OF GROUPS

	Original 200 Cases evaluated in		*Second 200 cases evaluated in*
	1951 (per cent)	*1952* (per cent)	*1952* (per cent)
Out of hospital	13	23	16.5
Good	45	25	32
Fair	11	24	23.5
Unimproved	29.5	26.5	25.5
Operative death	1.5	1.5	2.5
Total	100	100	100

was placed in seclusion for seven years prior to operation. Following his first transorbital lobotomy he made a remarkable recovery for two months, but then relapsed. A second lobotomy was done at the end of the third month and he again showed a rapid recovery that appeared more permanent. He became cheerful, obliging, eager to please, energetic, and a willing worker on the ward. Soon he was promoted to parole of the grounds. He continued to adjust perfectly and was allowed to leave the hospital three months after the second operation. A home with the Salvation Army was found for him. He is now self-supporting, sociable, willing to take advice, and has retained his natural drive to better himself. Recent evaluation shows that this patient has held a rather responsible position with a large corporation, and in recent months has changed his employment to a paint company for whom he now works. He is getting along well and earns $82.00 per week.

It is noteworthy to cite the changes that have occurred in the statistics of the first 200 cases in the past year and also to compare the second 200 cases with the earlier group. In table 9 the figures are given in percentages.

It may be observed that the greatest changes have occurred in the percentage of those who have left the hospital and in the rather pronounced increase of the fair improvement group. Both increases, however, presumably have caused a marked decrease in the good group. It is satisfying, nevertheless, that the unimproved group has grown smaller, no matter how small that decrease might be. It would seem that the second 200 cases are a little more heavily weighted in the fair group than in the good. The other differences, except for the increase in the mortality rate, are satisfactory.

TABLE 10
PERCENTAGE COMPARISON OF RESULTS ACCORDING TO SEX

	Original 200 cases evaluated in				*Second 200 cases evaluated in*	
	1951		*1952*		*1952*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Out of hospital	10	16	20	26	11	22
Good	60	30	25	25	28	36
Fair	6	16	27	21	31	16
Unimproved	22	37	26	27	28	23
Operative death	2	1	2	1	2	3

As far as the results according to sex distribution are concerned, it will be seen in table 10 that there has been a rather profound change in one year's time. The women of the original group seem to have continued to improve as evidenced by the decrease in the unimproved group, whereas a large number of men classified as good one year ago have apparently relapsed. Females of the second 200 are considerably ahead of the previous year's group in every way.

DISCUSSION

The statistics given in these tables illustrate the impressions the authors and other members of the hospital staff have had. It is felt that there is no question of the great improvement occurring in the group as a whole. It must be remembered that all of these patients had been considered hopeless and had failed to respond to all other types of therapy, including insulin and electroshock.

The average duration of illness for the group is almost 11 years, and most of the patients had previously been confined to small seclusion rooms for years. The operation is quite simple and is well suited for use in a large state hospital. The operations are performed on the wards. A team of nurses and attendants can easily be trained in the course of two to four operations. Four operations take but 15 minutes. The patients are treated postoperatively as if they had had simple electroshock therapy. Morbidity is very low, and only a small percentage of patients are incontinent for a week or so. There have been two or three instances of transient hemiparesis. From a psychiatric standpoint, we have succeeded in doing something at least for 72 per cent of our cases where all else had failed. This would be reward enough without considering the intense satisfaction of the families of those who have been helped, as well as the great gains made economically. We feel that 2 per cent is a small mortality for the results secured. Selection of cases on the basis of physical fitness has not been too strict, for we did not wish to deny any patient the chance of improvement. Actually most of the deaths occurred in patients considered excellent risks, the cause of death being intracerebral hemorrhage in all cases.

As of January 1, 1952, the per diem rate at the New Jersey State Hospital in Trenton was $3.18 per patient. At that rate, the 79 patients who have left the hospital will save the taxpayers of New Jersey $91,695.30 in a year's time. If they were average patients in this project, they would already have spent 10.8 years each at Trenton before they were operated upon, at a cost of about one million dollars. These were not average patients, however, if one considers the over-all hospital population; these were the most difficult care problems in the entire institution, and required more secure buildings, special equipment, and more psychiatric personnel for their care, all at higher cost. As far as those patients still in residence at Trenton are concerned, in excess of 200 cases have improved, more than half of these greatly improved. None of these patients is in seclusion and most are working around the hospital. Many produce

in work much more than the cost of their maintenance. There are no figures available to illustrate the money conserved in caring for these patients, but it is undoubtedly far in excess of the amount saved in those released from the hospital. The economic factors are of extreme importance when one considers that over one-half of all hospital beds in the United States are occupied by mental patients.

We are unable to explain the greater success apparently gained in the female group as compared to the male.

It is quite gratifying that improvement has continued in the first 200 cases in the second postoperative year.

SUMMARY

Four hundred cases of transorbital lobotomy are reported; there was marked improvement in approximately one-half of the cases and some improvement in another 25 per cent of chronically disturbed patients.

The results according to diagnosis are indicated.

It is urged that this type of operation be considered for all chronically disturbed patients.

The economic advantages in the improvement of such a group are stressed.

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If an individual suddenly has an epileptic convulsion for the first time, for which no cause can be discovered, central or peripheral, it is probably the commencement of epilepsy. Whether it is so or not can only be conclusively decided by the occurrence of another fit. Both patient and doctor anxiously ask: If this is epilepsy, when may another fit be expected? After how long a period of freedom is the expectation justified that no other fit will occur? No exact answer to this question can be given on account of the great variations in the interval between the first and second fit, the modifying effect of treatment in postponing or preventing the second fit and because we have no means of ascertaining, on any considerable scale, the frequency with which a single epileptic fit occurs without successors. But some help in forming an opinion may be obtained by comparing the relative frequency of interval between the first and second severe fits in a series of cases. Accurate facts on this point could be ascertained in only 160 cases.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Cerebral Lipiodol Granuloma

A. Morello, M.D., and I. S. Cooper, M.D.*

LIPIODOL is often used to visualize roentgenologically the cutting plane in which prefrontal lobotomy has been performed. The amount of the radiopaque dye usually employed is about 1 cc. injected into each side. Some surgeons imbed Gelfoam with Lipiodol in order to have more information about the direction of the cutting plane. In the same way, the dye is employed in cases of topectomy. Its use has also been advised as an aid in diagnosis of postoperative complications; for example, Lipiodol injected through operative incisions has been used to outline expanding lesions such as hematoma or abscess by depositing itself around or in such a lesion, which can then be demonstrated roentgenologically.

Radiologic examination of the skull and the spine performed about four months after lobotomy in which this preparation was injected into the cerebral hemispheres shows that in a high percentage of cases Lipiodol has not been absorbed and is scattered in the cerebral and spinal subarachnoid space as well as in the ventricles. We have recently concluded that instillation of the dye into the brain is not a justifiable procedure if other methods can be substituted. Aside from the risks involved, in cases of lobotomy it provides inadequate information and is also inconvenient to use. Because of its great density and specific weight it diffuses very poorly and tends to collect in drops at the most dependent places (figure 1). Consequently, in many cases only a part of the cutting plane is visualized, particularly if the x-rays are not taken immediately after the operation. In a series of 100 cases recently reviewed, demonstration of the cutting plane with Lipiodol was good in 10 per cent, satisfactory in 45 per cent, and unsatisfactory in 45 per cent. In a very high percentage of cases the dye had spread into the ventricles and the subarachnoid sulci before x-rays were taken. Furthermore, postoperative radiologic tests such as pneumoencephalograms and arteriograms are often unsatisfactory because of interference with roentgenologic visualization of the ventricles or cerebral blood vessels (figure 2).

Following is the report of a case of Lipiodol granuloma in the frontal lobe, illustrating that the dye may be responsible for serious reactive lesions.

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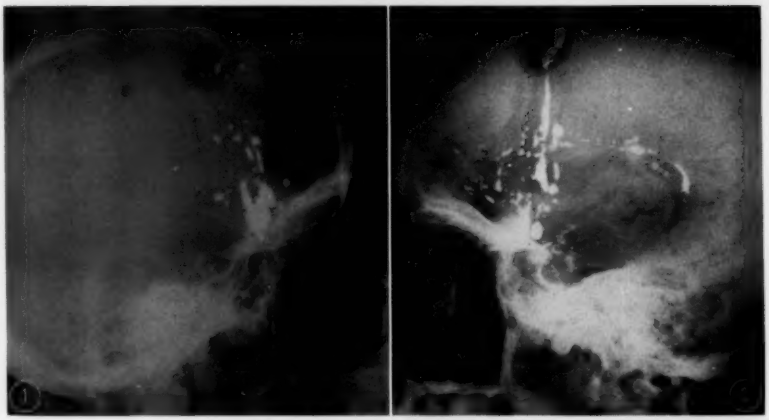

FIG. 1. Roentgenogram demonstrating intracerebral Lipiodol four months after lobotomy. Note droplets which have spread out of original plane of leukotomy.

FIG. 2. Lateral view of pneumoencephalogram demonstrating interference with interpretation of film caused by intracerebral Lipiodol.

A substitute technic to outline the cutting plane of prefrontal lobotomy is also described.

CASE REPORT

A 31 year old colored woman was admitted to Central Islip State Hospital on November 26, 1943, with a diagnosis of dementia precox, catatonic type. Despite several series of electroshock therapy, the patient did not improve and remained overactive, impulsive, and assaultive. She was referred for a prefrontal lobotomy which was performed on November 5, 1951. No improvement was noticed, and on August 1, 1952, the patient was submitted to a second prefrontal lobotomy. The white matter was cut further posteriorly than the first time. This time Lipiodol, 1 cc. per side, was used to visualize the cutting plane.

The patient had an uneventful postoperative course, but about ten days later the left operative incision appeared infected. The temperature was slightly elevated (100° F.) for one day. The wound was opened superficially and irrigations with penicillin were carried out daily, with antibiotics given parenterally. A culture revealed the presence of Staphylococcus aureus. Her general physical condition was good and the neurologic examination was negative. In a period of two weeks the wound appeared dry and there was no sign of further infection. At this time an additional 1 cc. of Lipiodol was injected into the left lobotomy incision in order to investigate radiologically the likelihood of a sinus tract or brain abscess. Three days later the patient became hemiplegic on the right side and Jacksonian epileptic seizures occurred on that side. Minor attacks were also observed.

Because focal seizures persisted the patient was operated upon on September 8, 1952, with a tentative diagnosis of abscess of the frontal lobe. On opening of the dura the cortical gyri appeared very pale. An incision of the cortex was made with an electric scalpel and a small, hard, yellowish nodule, situated deep in the lobe and not sharply separated from the surrounding tissue, was easily excised. In the white matter around it many cyst-like cavities containing yellowish fluid were seen. These were opened and the fluid was

FIG. 3. Microphotograph of Lipiodol granuloma. Note foreign body giant cells.

suctioned. One of them was seen to be communicating with the frontal horn of the lateral ventricle. The bone flap was removed and the scalp incision was partially sutured in order to leave in place a Vaseline gauze drainage, which was completely removed a few days after the operation. During the postoperative period irrigations of the wound with penicillin were performed daily and the wound healed completely in four weeks. The fluid removed from the cavities during the operation demonstrated no white cells or bacteria. The cultures were also negative.

Histologic examination showed the following: The peripheral stratum of inflamed cerebral cortical tissue was occupied partly by necrotic matter which included deposits of a calcific substance, and partly by a vascular and congested granulomatous tissue of loose texture which was intensively infiltrated by inflammatory cells of mononuclear type. Scattered in various parts, but denser in local areas of the granuloma, were multiple nucleated giant cells of foreign body type. In these locations, clumps and fragments of a light-refractile yellow and brown crystalloid substance lay in interstitial spaces and occasionally were found within the body of the macrophages. The granulomatous tissue merged imperceptibly with the glial tissue (figure 3).

DISCUSSION

The peculiar operative findings suggested and the microscopic report confirmed the fact that the pathologic alterations were secondary, at least in part, to the use of Lipiodol. This illustrates the desirability of avoiding instillation of a radiopaque dye into the brain, if a different method can be used to identify roentgenologically the cutting plane of prefrontal lobotomy.

Since the surgical procedure reported in this patient, another method has been used to visualize the cutting plane of prefrontal lobotomy. A portable x-ray unit, properly covered by sterile drapes, is placed close to the operating table. During operation the head of the patient lies on a head rest consisting of a flat piece of metal, 8 x 6 inches large. The patient's eyes are covered with

FIG. 4. Preparation of patient in present method of roentgenographic demonstration of plane of leukotomy.

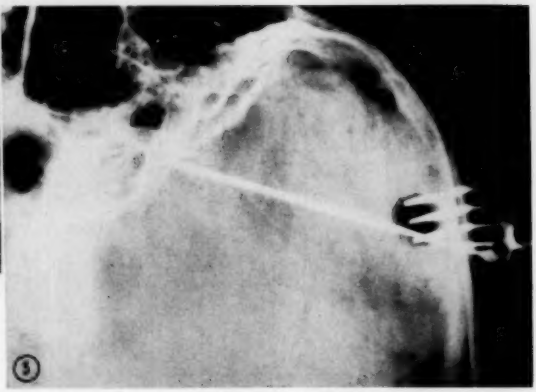

FIG. 5. Roentgenographic demonstration of ventricular needle plane of leukotomy.

Vaseline gauze and a long strip of adhesive tape, 2 inches wide, is passed around the head and the head rest, so that the head remains fixed (figure 4). After lobotomy is performed, the leukotome or a ventricular needle is held in place and an 8 x 10 inch x-ray cassette, mounted on a Mayo stand covered with a sterile pillowcase, is placed against the head of the patient and a lateral view taken. The stand has a handle by which the surgeon can easily regulate the height without being contaminated. This technique applies to prefrontal lobotomies with the so-called superior approach.

Figure 5 shows one of the roentgenograms of the present series. A standard lobotomy was performed in this case and the leukotome is seen in relation to the sphenoid ridge.

SUMMARY

Certain drawbacks are encountered in the use of intracerebral injection of radiopaque dye to demonstrate roentgenologically the cutting plane of a prefrontal lobotomy. In our experience such a visualization is not always accurate or adequate. Moreover, the dye is still present months after the injection and tends to diffuse throughout the intracranial cavity. A case of Lipiodol granuloma is reported to illustrate the possible adverse effect of this substance when injected intracerebrally.

A technic for roentgenologic visualization of the plane of lobotomy which does not depend upon the use of a contrast medium is described.

Effect of Themisone and Phenurone on Electrically-induced Seizures in the Salamander

Joseph J. Peters, Ph.D., and A. R. Vonderahe, M.D.

MATERIALS AND METHODS

The salamanders used in this investigation were adults of the species, *Triturus viridescens*. To evoke a seizure, a Grass model 3C stimulator was used to administer a biphasic current, 60 cycles per second, 20 milliseconds pulse duration, 100 volts, for 0.2 seconds. Shocks of a longer duration, for example 0.5 seconds, did not demonstrate the anticonvulsant properties of the drugs as conspicuously as the briefer shocks. Bárány and Stein-Jensen reported a similar relationship between duration of shock and anticonvulsant effects of some drugs in their studies on rabbits.[1] Shocking electrodes consisted of modified Grass electrode disks trimmed to a square shape, 5 mm. by 5 mm. Electric paste was used in applying them to the eyeballs. The resistance was between 10,000 and 11,000 ohms. Recordings were obtained with a Grass model III D, four-channel electroencephalograph. The electrodes were stainless steel needles inserted into the skull over the left olfactory and right cerebral lobes. Both Themisone (acrolactamide) and Phenurone (phenylacetylurea) were injected intraperitoneally, 2 mg. per gram of body weight, in a suspension of cotton seed oil which contained 80 mg. of the drug in 1 cc. of oil. The control animals received no medication or simply an injection of oil.

To investigate the anticonvulsant properties of a drug, the following routine procedure was adopted. All salamanders were given five shocks at intervals of approximately two to four hours on the same day. The experimental animals received the drug one hour before the third shock, and subsequent shocks were given one, three, five, and nine hours after the injection of the drug. Sample electroencephalograms were obtained from each group of animals. Motion pictures were used to facilitate a detailed study of convulsive movements.

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Aided by a grant from the United States Federal Security Agency, National Institute of Health, Division of Neurological Diseases and Blindness.

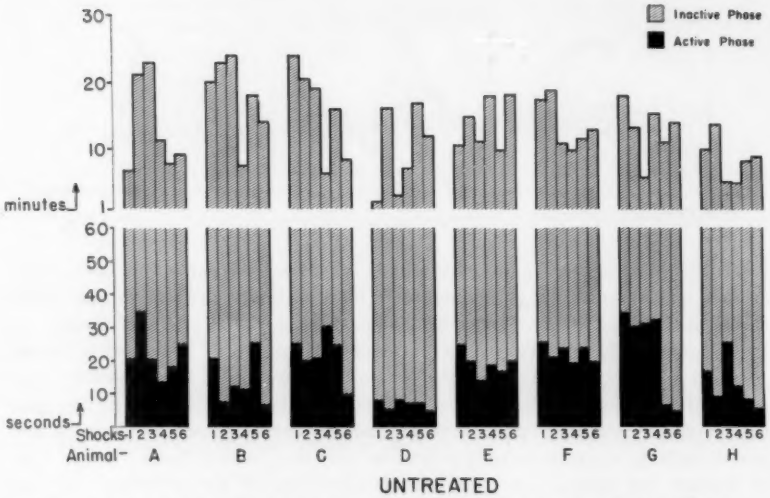

FIG. 1. Duration of phases after electric stimulation in salamanders given no medication. Shocks 1, 2, 3, 4, and 5, two hours apart; shock 6, four hours after shock 5. Letters A to H indicate different animals.

OBSERVATIONS AND RESULTS

Behavior of Untreated Salamanders during Induced Seizures

Although convulsive movements differ somewhat from animal to animal and from seizure to seizure, it is noteworthy that a particular pattern of seizure may be retained and with some exceptions predicted for an individual salamander when four or five seizures are induced on the same day at intervals of about two hours. The routine procedure described under materials and methods takes advantage of this fact, since it uses the first two shocks to determine the general pattern and duration of the stages of the seizure for a particular salamander, and then utilizes the subsequent three shocks after administration of the drug to evaluate its effects on the type of seizure manifested in the first two shocks.

During the time of actual electrical stimulation the salamander undergoes a stiffening and quiver of the entire body, especially noticeable in the vertebral column, appendages, and tail. Since there is some doubt as to the exact relationship which exists between the commonly described tonic-clonic phases of mammalian seizures and those of the salamander, the behavior after the shock was simply divided into two conspicuous phases, an active and an inactive phase (figure 1). In the salamanders receiving no drugs, the active phase occurs immediately after the shock, lasts from three to 40 seconds, and is characterized by convulsive movements. Occasionally this active phase is interrupted by a few seconds of apparent inactivity. The active phase is

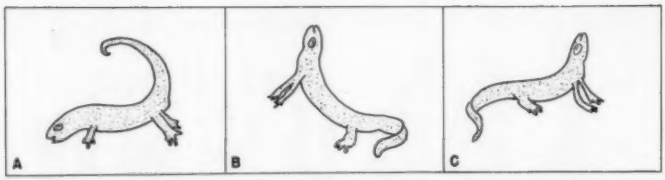

FIG. 2. Some typical postures assumed by salamanders during the active phase following electrical shock stimulation.

typically followed by an inactive phase which lasts from a few seconds to 20 or more minutes, and is characterized by a motionless stupor during which the animal shows little or no escaping response to the stimulus of touch.

Although salamanders exhibit a variety of convulsive movements during induced seizures, there are a few general patterns of activity which occur repeatedly and afford a basis for classifying the seizures into four or five general types. A common pattern of seizure is that in which the salamander passes through a posture which resembles that of a rearing horse. In this type of seizure the animal undergoes brief vibrations of the vertebral column, together with clonic-like movements and extension of limbs, digits, and tail (figure 2A). The head is then slowly elevated dorsally until it achieves an angle of about 60 degrees with the long axis of the body, the forelimbs simultaneously extend ventrocranially, the animal staggers forward a few steps, stops, and with the forelimbs paws the air four or five times. The salamander concludes this active phase of the seizure in one of two ways: either it flexes the limbs and comes to rest on its belly, or the opisthotonus curvature of the vertebral column becomes so excessive that the forelimbs are elevated from the table (figure 2B). Eventually the salamander supported by the hind legs and the base of the tail falls backward or topples to one side. The strained opisthotonus position may be retained for 15 or 20 seconds. Finally the animal relaxes, becomes motionless, and the active phase ends.

Not all salamanders undergo the "rearing" type of active phase. Some animals perform writhing movements of the vertebral column immediately after the shock, together with clonic vibrations of limbs and base of tail. This rapid activity is sometimes followed by a slow dorsal elevation of the head, and an extreme extension of fore and hind limbs, either laterally or ventrally (figure 2C). Finally the salamander becomes motionless and comes to rest on its side or belly.

The active phase may exhibit another pattern in which the salamander runs away rapidly, immediately after the shock, and undergoes what seems to be an escaping reaction which lasts from 10 to 30 seconds. A less frequent pattern of the active phase of a seizure is one in which the salamander executes such violent swimming or leaping movements that it is hurled through the air for a short distance. This rapid activity lasts about five seconds. However, after these sudden bursts of activity the animal is not normal. When it

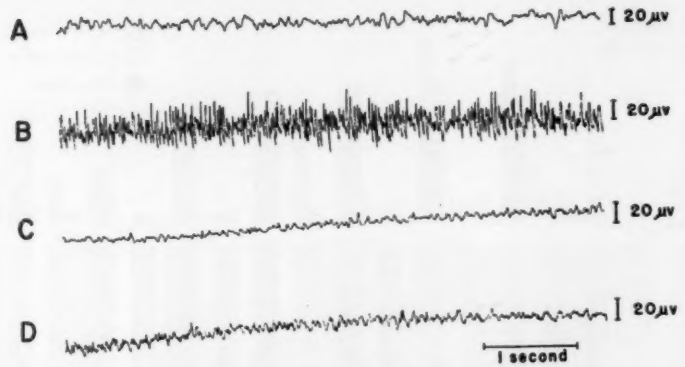

FIG. 3. Electroencephalograms of salamanders. A. EEG of normal untreated animal before shock. Records B, C, and D begin ten seconds after electrical stimulation. B. EEG of animal given only cotton seed oil three hours previously. C. EEG of animal given Themisone two hours previously. D. EEG of animal given Phenurone three hours previously.

stops, it will come to rest on its belly and enter the stupor of the inactive phase.

Although the active seizure patterns of most salamanders can be classified into one of the general types described above, it should be noted that some salamanders undergo seizures which are combinations of various convulsive movements. Subdivision into other categories seems unnecessary at present.

Cessation of movement after the shock was an arbitrary criterion which indicated the beginning of the inactive phase of the seizure. The salamander was judged as remaining in this inactive phase as long as it failed to walk away a distance of eight inches, either spontaneously or under the influence of a stimulus of touch. If the animal took only a few steps with each stimulus, the animal was considered as still being in the inactive phase, with only a partial return to normal alertness and behavior.

During the inactive phase handling or stimulating the salamander by touch evoked several types of responses. The corneal reflex was present 45 seconds after the shock. Some salamanders exhibited hypersensitivity when they twitched violently in response to such a gentle stimulus as a shadow cast across the eye. A repeated touching along the vertebral column sometimes resulted in a tense opisthotonus position which persisted for several minutes. During the 15 minutes following the shock a test for the righting reflex gave various results. Sometimes this reflex asserted itself promptly, sometimes slowly, at other times it was absent. This last abnormality may have been due to the fact that the shock was applied near the semicircular canals.

Effect of Themisone on Induced Seizures

Themisone modified both the behavior and the electroencephalogram of salamanders subjected to electric shock stimuli (figure 3 and 4). One hour after the administration of the drug beneficial effects were evident in both the active

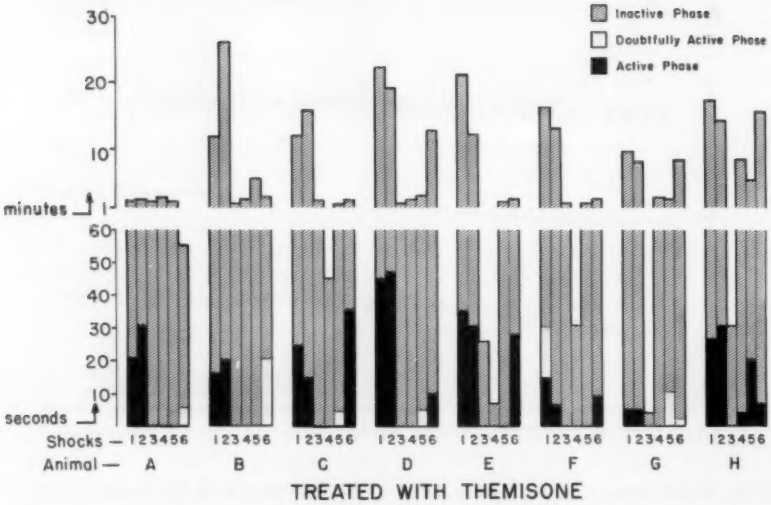

FIG. 4. Duration of phases after electric shock stimulation in animals given Themisone. Shocks 1 and 2, two hours apart. Shocks 3, 4, 5, and 6, one, three, five, and nine hours, respectively, after injection of Themisone. Letters A to H indicate different animals.

and inactive phase. Under the influence of Themisone the active phase was mild or absent; also, the inactive phase was considerably shortened or almost absent. After the shock some of the salamanders simply walked away with good coordination; others underwent a few writhing movements and then either walked away or remained motionless for a few seconds before doing so; still others were motionless for a few seconds and then walked away either spontaneously or when stimulated by touch. A comparison of the electroencephalograms of the control animals after the shock and those of the salamanders treated with Themisone shows an absence of or a considerable diminution of spikes in the animals receiving the drug (figure 3). Some of the apparent spikes in the electroencephalographic record of treated salamanders are probably due to muscle artifacts brought on by escaping reactions following the shock. The anticonvulsant effects of a single dosage of Themisone were still evident in some of the salamanders nine hours after administration.

It should be noted that a few hours after injection of Themisone some of the salamanders exhibited a temporary unsteadiness in gait and a certain amount of sluggishness. A somewhat similar side-effect was reported in human treatment.[2] But by the next day these abnormal effects were absent.

Effect of Phenurone on Induced Seizures

Salamanders treated with Phenurone showed a marked change in both behavior and the electroencephalogram after an electric shock stimulus. Three

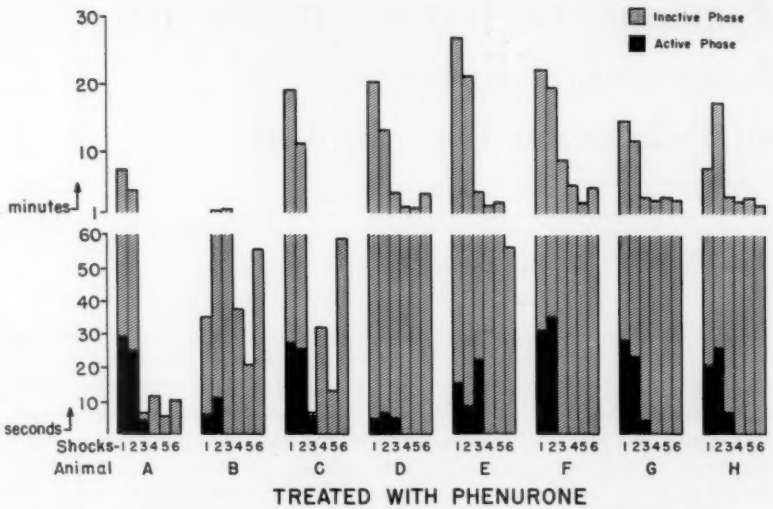

FIG. 5. Duration of phases after electric shock stimulation in animals given Phenurone. Shocks 1 and 2, two hours apart. Shocks 3, 4, 5, and 6, one, three, five, and nine hours, respectively, after injection of Phenurone. Letters A to H indicate different animals.

hours after the administration of the drug, the active phase of an electrically-induced seizure was either absent or reduced in violence and duration; similarly, the inactive phase was either absent or considerably shortened (figure 5). The electroencephalogram of salamanders given Phenurone showed very few or no spikes after electric shock stimuli (figure 3). Although the anticonvulsant properties of Phenurone were already manifest one hour after administration, a more effective result was noted at the end of three hours. Twenty-four hours after administration the anticonvulsant action was still evident in some salamanders but in a diminishing degree.

SUMMARY

The behavior of salamanders during electrically-induced seizures is described in terms of an active and an inactive phase. Both Themisone and Phenurone inhibit the violent active phase of a seizure and diminish the duration of the stupor or inactive phase typically found in untreated salamanders. Phenurone acts more slowly but its effect lasts longer than that of Themisone. Themisone, unlike Phenurone, produces a temporary unsteadiness in gait and some sluggishness.

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Experimental Intraventricular and Intracerebral Injection of Polymyxin B in the Cat

Paul Teng, M.D.

POLYMYXIN B (Aerosporin) is an effective antibiotic agent against infections caused by the gram-negative bacillus, such as *Hemophilus pertussis, Escherichia coli, Eberthella typhosa, Shigella dysenteriae, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Hemophilus influenzae.*[1-3] Nevertheless its clinical use by parenteral administration is limited by the nephrotoxin which it contains. In selected cases, whenever systemic polymyxin is indicated, it should be given with caution, using a carefully estimated dosage, and its use followed by close observation for changes in the urine and repeated tests for renal function. Thus used, satisfactory results can be obtained without any significant injury to the kidney. It has been repeatedly administered both by the parenteral and by the intrathecal route in the treatment of purulent meningitis caused by *Ps. aeruginosa, E. coli,* or *H. influenzae.* A large intrathecal dose of polymyxin has produced neurologic abnormalities both in experimental animals and in patients.

In the medical literature there is no record of experimental or clinical observations made on the intraventricular or intracerebral injection of this antibiotic. The aim of this experiment was to test the toxicity of polymyxin B applied directly to the brain. The antibiotic was instilled into the left lateral ventricle or into the left cerebral hemisphere in nine cats. The following method has been used, and the results that were observed are reported.

METHOD AND MATERIALS

Twelve normal adult cats weighing from 2 to 3.7 kg. were used in this study (table 1); three of these were controls. The animals were anesthetized by the intravenous injection of sodium Nembutal, 30 mg. per kg. of body weight. The head was shaved, the scalp prepared with iodine and alcohol, and the operating field draped with sterile towels. A left parasagittal scalp incision, about 1¼ inches long, was made in the frontal region and the temporal muscle and periosteum were separated from the underlying skull. An opening was trephined in the left frontal parasagittal area.

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This study was aided by a grant from the Dazian Foundation.

TABLE 1

INJECTION OF 2,500 OR 5,000 UNITS OF POLYMYXIN B IN 0.02 CC. OF NORMAL SALINE SOLUTION INTO THE LEFT LATERAL VENTRICLE OR INTO THE LEFT CEREBRAL HEMISPHERE IN THE CAT

Cat No.	*Body weight in kilo*	*Site of injection*	*Anesthesia*	*Injected material*	*Duration of survival*	*Reaction and pathologic finding*
1	3.7	Left lateral ventricle	Yes	Polymyxin B 2,500 units	10 days	No reaction. Minimal softening in the white matter of the left frontal lobe around the tract of the ventricular puncture.
2	3.5	" " "	Yes	" "	1 month	No reaction. Minimal softening in the subcortical white matter, around the upper portion of the tract of the ventricular puncture through the left frontal lobe.
3	3.0	Left cerebral hemisphere	No	" "	10 days	No reaction. An area of softening, 5x4x2 mm., in the white matter below and lateral to the left lateral ventricle.
4	3.5	" " "	Yes	Polymyxin B 5,000 units	10 days	No reaction. An area of softening, 3x2x3 mm., in the lateral part of the left thalamus and opened into the 3rd ventricle.
5	3.0	" " "	No	Polymyxin B 2,500 units	1 day	Transient weakness in the right limbs, rapid respiration and pulse rate and vomitings. Hemorrhage in the left thalamus, internal capsule, and in the region of the left hypothalamus.
6	2.0	" " "	No	Normal saline 0.05 cc. (control)	1 day	No reaction. Small hemorrhage in the subcortical white matter of the left frontal lobe, above the corpus callosum.
11	3.5	" " "	No	Polymyxin B 5,000 units	1 month	No reaction. Minimal softening in an area lateral to the left anterior horn of the lateral ventricle.
12	3.2	" " "	No	Normal saline 0.05 cc. (control)	10 days	No reaction. Negative finding in the brain.
13	3.0	Left lateral ventricle	Yes	Polymyxin B 5,000 units	1 month	No reaction. Normal brain.
14	3.0	" " "	Yes	" "	1 day	No reaction. A tract was found through the left anterior part of the corpus callosum.
15	2.8	Left cerebral hemisphere	No	Normal saline 0.05 cc. (control)	1 month	No reaction. Normal brain.
16	3.5	" " "	No	Polymyxin B 5,000 units	1 day	No reaction. Minimal hemorrhage in the upper frontal subcortical white matter.

For the intraventricular injection this trephined opening was further enlarged to the size of about ¾ of an inch. Through the thin and transparent dura mater the sulcus cruciatus, sulcus ansatus, sulcus suprasylvius anterior, and the sulcus lateralis were identified. Thereafter, an intradermal needle was lowered perpendicularly into the left cerebral hemisphere at the point 1 cm. posterior to the sulcus ansatus and 0.5 cm. lateral to the midline (figure 1). At a depth of about 1 to 1.2 cm. the needle entered the lateral ventricle, into which 2,500 or 5,000 units (equivalent: 1 mg. = 10,000 units; 1 microgm. = 10 units) of polymyxin B in 0.05 cc. of physiologic saline solution, pH 6,

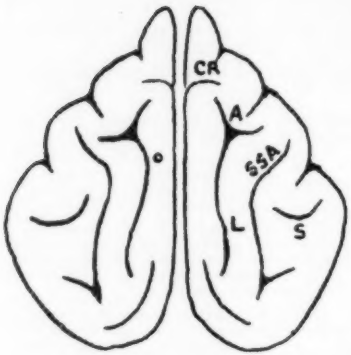

FIG. 1. Topography of cat's brain. O indicates the site of injection; CR, sulcus cruciatus; A, sulcus ansatus; SSA, sulcus suprasylvius anterior; L, sulcus lateralis; and S, sulcus pseudosylvius.

were instilled from a tuberculin syringe in two to four seconds. Then the needle was withdrawn and the wound was closed with silk. The intraventricular injection was tried in five cats. Later, autopsy findings showed that in one instance the attempt failed and the injection was intracerebral.

In order to eliminate the anticonvulsant effect of sodium Nembutal, four cats were given an intracerebral instillation of the same amount of polymyxin B under no anesthesia. The trephination of the skull was done 24 or 48 hours prior to the intracerebral injection. Three other cats were used as controls, in which 0.05 cc. of physiologic saline solution without polymyxin B was injected into the left cerebral hemisphere.

The animals were divided into three groups. Each group consisted of four cats including one control. The experimental cats received either an intraventricular or an intracerebral injection of 2,500 or 5,000 units of polymyxin B (table 1).

The cats of group 1 were sacrificed in 24 hours, group 2 at ten days, and group 3 at four weeks after the intracerebral or intraventricular instillation of the tested material. The cerebrum, the cerebellum, the brain stem, and the upper cervical spinal cord as well as their meninges were removed and fixed in 20 per cent formalin solution.

OBSERVATIONS

After the intracerebral or intraventricular injection of polymyxin B, each cat was observed for three hours before it was sent back to its cage. Thereafter, each animal was examined and observed daily until it was killed at the scheduled time with a large intravenous dose of sodium Nembutal.

Neither the intraventricular nor the intracerebral injection of 2,500 or 5,000 units of polymyxin B, with or without intravenous sodium Nembutal anesthesia, produced muscular twitchings, convulsions, paresis, or any other untoward reaction during the acute or chronic stage of this experiment in eight cats. In only one animal a severe reaction was observed four minutes

after the intracerebral instillation of 2,500 units of polymyxin B. This cat became restless; its pupils were markedly dilated; its gait was unsteady; and its limbs were weak. The weakness was found to be more pronounced in the limbs of the right side than those of the left, and it fell frequently to the right. Its respirations were panting, 96 per minute, and its heart beats were rapid and forceful, 178 per minute. Eleven minutes later it vomited repeatedly. The vomitus was the gastric contents of the meal that had been ingested before the experiment. Simultaneously it evacuated its rectum twice. Forty minutes after the injection this cat was unable to stand on its hind legs. However, its respiration and pulse rates gradually returned to normal. The size of the pupils also returned to normal. Three hours later the weakness of the hind legs was gradually disappearing. The next day the animal was seen walking with no apparent weakness of the limbs. Examination showed that there was no impairment of the placing or hopping reflexes. Pin pricking of the paws revealed no disturbance of pain sensation. Later, sections of the brain showed that the injection was in the internal capsule, the thalamus, and the hypothalamus of the left side.

The intracerebral injection of 0.05 cc. of physiologic saline solution to the three controls produced no untoward reaction.

Autopsy findings. Group 1. The sections of the brains of cats numbers 5, 6, 14, and 16, killed 24 hours after the intraventricular or intracerebral injection of polymyxin B, revealed the following findings: The brain of cat number 5, which received an intracerebral injection of 2,500 units, showed an area of hemorrhage, measuring 1.2 x 4 x 3 mm., and involving the internal capsule, thalamus, and the hypothalamus of the left side. This cat developed the alarming reaction described above. Cat number 16 was given 5,000 units of polymyxin B by the same route. Minimal hemorrhage was found along the tract of the needle in the white matter of the left frontal region. Cat number 14 had received 5,000 units in the left lateral ventricle; a thin needle tract was located in the left anterior lateral portion of the corpus callosum, but there was no evidence of hemorrhage. The brain of the control exhibited an elongated small hemorrhagic area in the subcortical white matter of the left frontal area. The leptomeninges and the cerebral cortex of all four specimens were congested.

Group 2. Cats numbers 1, 3, 4, and 12 were killed ten days after the intracerebral or intraventricular instillation of the tested material. The brains of all four animals appeared normal externally. Cat number 1 was given an intraventricular injection of 2,500 units of polymyxin B. Sectioning of the brain disclosed a thin linear area of brownish discoloration in the white matter of the left frontal region. This tract passed through the left lateral anterior portion of the corpus callosum into the left lateral ventricle. The brain of cat number 3, into which 2,500 units of polymyxin B had been instilled, showed an area of softening, measuring 3 x 2 x 3 mm., located in the left thalamus and subthalamus. The lesion also involved the left wall of the third

FIG. 2. Section of brain showing hemorrhage in the area of softening caused by the intracerebral injection of 2,500 units of polymyxin B in 0.05 cc. of normal saline solution. Lesion involves the left thalamus and the wall of the third ventricle. Animal killed ten days after the test. (Hematoxylin-eosin stain.)

ventricle (figure 2). There were no abnormal findings revealed in the brain of the control.

Group 3. Cats numbers 2, 11, 13, and 15 were killed one month after the experiment. The leptomeninges and the surface of the brain of all four animals looked normal. Sections of the brain of cat number 2 revealed a thin linear area of softening with yellowish discoloration in the white matter of the left frontal lobe. It was perpendicular to the anterior lateral portion of the corpus callosum, through which a tract was seen passing into the left lateral ventricle. This cat had been given an intraventricular injection of 2,500 units of polymyxin B. The brain of cat number 11, into which 5,000 units of polymyxin B had been instilled, showed a curve-shaped area of softening, 3.5 x 2 mm., lateral to the wall of the anterior horn of the left lateral ventricle. There were no abnormal findings in the brain of cat number 13, into which an intraventricular injection of 5,000 units of polymyxin B had been administered. The brain of the control looked normal.

Microscopic examination. Blocks were taken from the area of the brain which showed gross pathologic change and embedded in paraffin, cut at 5 to 6 microns and stained by the hematoxylin-eosin method.

Group 1. Brain sections of the four cats in Group 1, including the control, showed acute inflammatory changes with polymorphonuclear leukocyte infiltrations of the leptomeninges, especially in the region of the operated area and in the subarachnoid space. The perivascular spaces of occasional blood vessels penetrating into the superficial portion of the parenchyma of

the brain showed infiltration by polymorphonuclear leukocytes. Hemorrhage was found at the site of the intracerebral injection in three cats and the control. The white matter surrounding these areas was infiltrated by polymorphonuclear and a few mononuclear leukocytes. Similar changes were observed in the tissues along the tract of the intraventricular puncture in cat number 14. The choroid plexus of the third and lateral ventricles and the ependymal lining of the ventricular system looked normal in all four specimens.

Group 2. Brain sections of the four cats in Group 2 showed lymphocytic and polymorphonuclear cell infiltrations of the leptomeninges. Similar cells were found in the subarachnoid space. At the site of the intracerebral polymyxin injection, an area of softening with numerous vacuolated microglial cells and scattered lymphocytes and polymorphonuclear leukocytes were seen. A thin layer of the neighboring tissues was edematous and congested. There were many phagocytic cells containing dark brownish pigments. In the brain of cat number 4 a fresh hemorrhage was found inside the softened area. This was probably the result of manipulation when the brain was being removed from the skull. In addition to the above described findings, the sections showed that the softened area broke into the left lateral ventricle of cat number 3 and through the wall into the third ventricle of cat number 4. In both cases the choroid plexus of the third and lateral ventricles was found markedly congested with dilated vessels. The ependyma as well as the subependymal tissues were infiltrated by lymphocytic and polymorphonuclear cells. In cat number 1, a minimal softening was found in the white matter of the left frontal lobe along the tract of the intraventricular puncture. The choroid plexus of the third and lateral ventricles of this animal looked normal.

Sections of the brain of the control showed only some lymphocytes and a few polymorphonuclear leukocytes in the leptomeninges and in the subarachnoid space.

Group 3. The sections of the brain of cat number 13 and of the control revealed no abnormality. A small area of softening was found in the white matter of the left frontal lobe in cats numbers 2 and 11. The softened area in cat number 2 was of linear shape and along the tract of the intraventricular puncture. There were numerous vacuolated microglial cells in the outer zone of the softened area in both cats numbers 2 and 11. Gliosis was seen in the periphery of this area.

DISCUSSION

This experiment showed that the intraventricular or intracerebral injection of 2,500 to 5,000 units of polymyxin B in eight cats produced no clinical toxic reaction. Only one animal developed vomiting, diarrhea, increase of respiratory and pulse rates, and a transient weakness of the limbs after an intracerebral injection of 2,500 units of polymyxin B in 0.05 cc. of physiologic saline solution. However, at autopsy it was found that the injection in this cat had been made into the left internal capsule and the region of the hypo-

thalamus. In the other animals instillation of 2,500 to 5,000 units of polymyxin B into the white matter of the cerebrum, the lateral ventricle, or into the thalamus, the lateral wall of the third ventricle, and the third ventricle was well tolerated. Yet this antibiotic is toxic to the brain tissue, as has been demonstrated by microscopic examination. Acute inflammatory changes were found in the brain tissues of cats in Groups 1 and 2 one to ten days, respectively, after the intracerebral injection of polymyxin B, and softening and gliosis were observed in Group 3 one month after the experiment.

Similar but more toxic reaction was observed in dogs when polymyxin B was injected into the cisterna magna.[4] The injection of 50,000 units of polymyxin B in 1 cc. of physiologic saline solution by the intracisternal route invariably caused death in three dogs of 22 to 35.2 lb. of body weight. A dosage of 10,000 units by the same route produced weakness of the hind legs with an unsteady gait and frequent falls in two experimental dogs. Five thousand units of polymyxin B injected into the cisterna magna of four dogs was well tolerated, and none of these animals showed any abnormal neurologic signs.

In the treatment of purulent meningitis, 50,000 units of polymyxin B have been administered indiscriminately by the intrathecal route in infants as well as in adult patients of over 150 lb. Survivals from these usually fatal types of meningitis caused by *E. coli*, *Ps. aeruginosa*, or *H. influenzae* have been recorded in the medical literature,[5–11] but the neurologic sequelae that have been produced by such large intrathecal doses of polymyxin B should not be overlooked. The sequelae which have been described include hypotonia of legs, weakness in the limbs, unsteady gait, incontinence or urinary retention, convulsions, and coma. It has been demonstrated in experimental animals that intracisternal injection of 10,000 units of polymyxin B in dogs causes degenerative changes of the anterior horn cells as well as the nerve roots of the spinal cord.[4] There is no doubt that this antibiotic is toxic to the tissues of the central nervous system when directly applied. Its toxicity is directly proportional to the amount used. Therefore, whenever it is indicated, the intrathecal dosage must be carefully estimated, depending upon the age and body weight of the patient. In the treatment of septic meningitis or ventriculitis caused by susceptible organisms, an intrathecal or intraventricular dosage of polymyxin B no greater than 1,000 units in infants or newborn, 5,000 units in children, and 10,000 units in adults, once or twice a day based upon the severity of the infection, should be used. The total amount of cerebrospinal fluid in a normal adult is 100 to 150 cc., and, in spite of the rapid absorption of the antibiotic form the subarachnoid space after an intrathecal instillation, 10,000 units of polymyxin B is able to maintain an adequate therapeutic level in the cerebrospinal fluid for ten to 12 hours.[4,5]

In the case of brain abscess caused by susceptible organisms, this antibiotic, in an estimated dosage of 10,000 units, should be instilled into the abscess cavity or into the cavity from which the abscess is surgically removed. This experiment has shown that injection of 2,500 to 5,000 units of poly-

myxin B in 0.05 cc. of physiologic saline solution into the normal brain of cats has produced no untoward clinical signs. The area of softening in the cerebral white matter is small in comparison with the dosage and the concentration of the antibiotic. For clinical use by the intracerebral or intraventricular route, the concentration should not exceed more than 5,000 units per cubic centimeter.

SUMMARY

1. Twelve cats, including three controls, were used in this experiment.

2. In four cats, 2,500 or 5,000 units of polymyxin B in 0.05 cc. of normal saline solution were injected into the left lateral ventricle under Nembutal anesthesia. None of these cats showed any toxic neurologic reactions. Sections of the brains of these animals revealed no significant changes.

3. Five cats were given an intracerebral injection of polymyxin B, 2,500 or 5,000 units, into the left cerebral hemisphere. One cat was injected under sodium Nembutal and the other four without anesthesia. Only one animal developed a reaction; sections of the brain showed that the injection was in the left thalamus, internal capsule, and the region of the hypothalamus.

4. Pathologic examination revealed acute inflammatory changes in the leptomeninges and minimal hemorrhage in the early stage of the experiment, and softening and gliosis in the area of the intracerebral instillation in the later stage.

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Neurocutaneous Syndromes in the M Kindred

A Case of Simultaneous Occurrence of Tuberous Sclerosis and Neurofibromatosis

William J. Schull, Ph.D., and Frank W. Crowe, M.D.

THE neurologic and cutaneous similarities observed in von Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis, and encephalotrigeminal angiomatosis (Sturge-Kalischer-Weber syndrome) have led to their identification as organic neurocutaneous syndromes. The early recognition of a familial concentration in the distribution of the first two diseases naturally suggested a genetic component in their etiology. The thesis, now generally accepted, that tuberous sclerosis and neurofibromatosis both represent instances of simple dominant heredity appears to have been first advanced by Siemens[1] and Preiser and Davenport,[2] respectively. The role of heredity in the etiology of encephalotrigeminal angiomatosis is still undefined.

As a further consequence of these neurologic and cutaneous similarities, Hintz[3] and others have proposed a common etiology for tuberous sclerosis and neurofibromatosis, the more common of these syndromes. The proponents of this point of view have cited the occasional occurrence of more than one of the syndromes in a given family as evidence of the validity of Hintz' conclusion. This point of view has been rigorously contended from its inception by Nieuwenhuisje[4] and later workers who deny that association implies a common etiology. The latter group asserts that these two syndromes are independent clinical entities and that the combination of these syndromes in a single family or individual is merely the result of the chance combination of two different genes in that family or individual.

CASE REPORTS

The proposita, that is, the index case of this kindred (figure 1), came to the attention of the authors as a consequence of a survey of neurofibromatosis conducted on 6,871 individuals in four Michigan institutions for the epileptic

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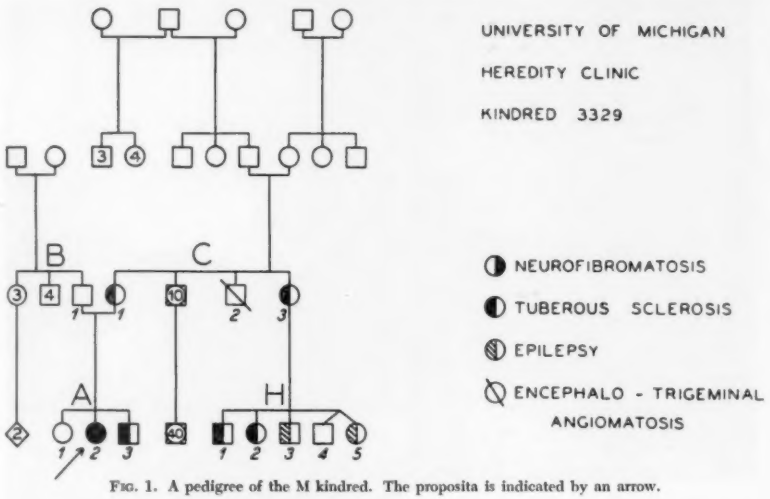
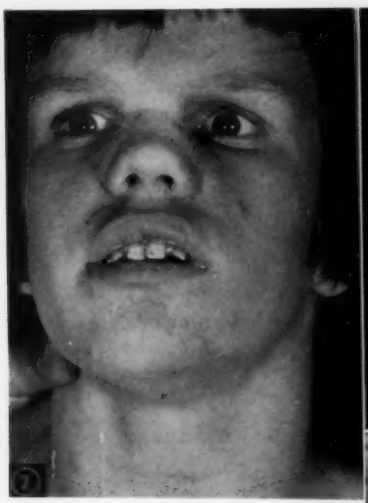


FIG. 1. A pedigree of the M kindred. The proposita is indicated by an arrow.

and/or mentally retarded. While this kindred has been previously reported by Dickerson,[5] additional evidence gained through the survey and through access to records not available in 1951 warrants a further report.

A-1: An 18 year old white female, born August 6, 1934, was admitted to a Michigan mental institution on April 10, 1941. There was a history of instrument delivery, normal development during early childhood, and no convulsive disorders. Cutaneous examination revealed no abnormal pigmentation or other stigmata of either tuberous sclerosis or neurofibromatosis. Intelligence quotient was 73, and electroencephalogram normal. The diagnosis was mental retardation.

A-2: Proposita of this kindred. A 15 year old white girl, born February 7, 1938, was admitted to a Michigan mental institution May 7, 1941. Delivery was reported to have been normal, but there were early manifestations of mental retardation. First recorded seizure was at the age of four. The intelligence quotient was 15 (Kuhlmann), and the electroencephalogram abnormal. Cutaneous examination revealed 12 café-au-lait spots exceeding 1.5 cm. (broadest diameter), with numerous smaller guttate areas of macular pigmentation. Multiple cutaneous tumors varying in color from white to violaceous were palpable; upon digital compression these tumors exhibited the "button holing" effect characteristic of neurofibroma. There were many colloidomas on the back and shoulders and a number of cutaneous tags were observed. Subungual fibromatosis was noted. Examination of the face disclosed typical adenoma sebaceum around the nasal alae, in the mentolabial fold, and on the forehead (figure 2). Roentgenograms of the skull (figure 3) revealed multiple sclerotic patches within the cranial vault and minimal intracranial calcifications. A tumor was excised from the right lumbosacral area. Grossly, this was a subcutaneous blue-gray translucent mass about 0.75 cm. in diameter. Histologically, the mass consisted of delicately whorled cells around multiple round areas which suggested nerve bundles. In one of these areas myelineated nerve fibers were present. Large irregular mast cells appeared among the proliferated elements (figure 4). The tumor was diagnosed as a neurofibroma, compatible with von Recklinghausen's disease. A second tumor, excised from the anterior thorax, was found to



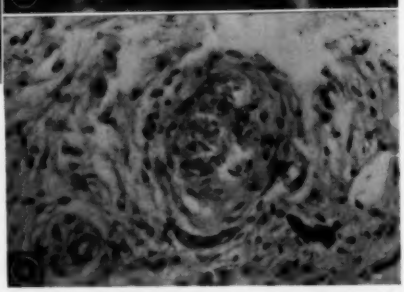


FIG. 2. The proposita of the kindred. Multiple adenoma sebaceum are clearly visible around alae of the nose, and in the mentolabial fold.

FIG. 3. Left lateral view of the skull of the index case showing sclerotic patches in the calvarium and areas of increased density.

FIG. 4. A photomicrograph of one of the tumors excised from the proposita. Hematoxylin and eosin stain.

be substantially the same on gross and histologic examination. This patient was diagnosed as having both neurofibromatosis and tuberous sclerosis.

A-3: A 13 year old white boy, born November 8, 1939, was admitted to a Michigan mental institution July 22, 1943. Delivery was reported to have been normal; mental retardation was obvious by 15 months of age. The time of onset of seizures was unknown. Cutaneous examination revealed no areas of macular pigmentation. Over the back and shoulders were numerous papular colloidomas, and one epithelial tag was noted in the left axillary line. Subungual fibromatosis was evident, as were characteristic adenoma sebaceum. Roentgenograms of the skull showed intracranial calcifications. The intelligence quotient was 19 (Kuhlmann), and the electroencephalogram abnormal. The diagnosis was tuberous sclerosis.

B-1: A 47 year old white male, the father of A-1, A-2, and A-3, was born March 25, 1906. He completed the fifth grade, but had always been a behavioral problem and had a long prison record. The prison hospital record indicated psoriasis as the only cutaneous abnormality. This individual could not be examined, but his intelligence quotient was known to be 77 (revised Army Alpha).

C-1: A 52 year old white female, the mother of A-1, A-2, and A-3, was born April 13, 1900. She was admitted to a Michigan mental institution July 17, 1941. Birth and development history were reported to be normal. She completed sixth grade at the age of 16. Facial lesions occurred at the age of 14 and seizures in the early twenties. Cutaneous

examination disclosed no areas of macular pigmentation or lesions other than several papular colloidomas, adenoma sebaceum, and subungual fibromatosis. Roentgenograms of the skull indicated intracranial calcifications. The intelligence quotient was 58, and the electroencephalogram abnormal. The diagnosis in this case was tuberous sclerosis.

C-2: A white male, born November 6, 1897, was admitted to a Michigan mental home November 18, 1909. He died on September 11, 1911, in status epilepticus. He was reliably reported to have had a right-sided facial hemangioma and marked mental retardation. Convulsions began on the third day of life and occurred approximately at monthly intervals thereafter. The presumptive diagnosis was encephalotrigeminal angiomatosis.

C-3: A white female was born in 1902 and died November 6, 1933, following the surgical removal of a glioblastoma multiforme. She was reported to have had dizzy spells and headaches from the age of 17. Lesions over the chin, about the alae of the nose, on the chest, and scattered elsewhere on the body were small, firm nodules varying from pinhead size to the size of a bean, the smaller ones whitish in color and the larger ones a pink color. Some of them were isolated and others were in groups. On almost every toe clusters of small firm, pink nodules were seen about the nails. These were similar to those nodules seen elsewhere on the body. One of the isolated nodules was examined histologically in 1932 and reported to be a fibrous papilloma. A 1933 report on roentgenograms of the skull recorded the presence of multiple sclerotic areas throughout the calvaria and calcifications in the region of the basal ganglia. The diagnosis in this case was tuberous sclerosis.

H-1: A 29 year old white male was born November 3, 1924, and admitted to a Michigan mental institution June 12, 1940. Mental retardation was manifested early in infancy, and seizures began at four months of age. Cutaneous examination disclosed no areas of macular pigmentation. Typical adenoma sebaceum and subungual fibromatosis were present. There was a phacoma of the left optic disk. Roentgenograms of the skull revealed scattered areas of increased density throughout the calvaria. The intelligence quotient was 19. The diagnosis was tuberous sclerosis.

H-2: A 26 year old white female was born July 2, 1926, and admitted to a Michigan state mental institution January 31, 1936. She was excluded from public schools because of poor progress. First known seizure occurred at the age of 17. Cutaneous examination revealed a single café-au-lait spot on the left suprascapular area. There were multiple nodular lesions surrounding the nasal alae and in the mentolabial fold; a prominent telangiectatic element was noted in the adenoma sebaceum. Many flat papular areas were observed on the back and in the lumbosacral area. Subungual fibromatosis was present. Phacomas were visible in both fundi. Roentgenograms of the skull revealed areas of sclerotic bone in the calvaria and calcifications in the region of the basal ganglia. The intelligence quotient was 48 and the electroencephalogram abnormal. The diagnosis was tuberous sclerosis.

H-3: A 25 year old male, born December 30, 1927, was admitted to a Michigan state mental institution January 31, 1936, and released on probation in 1949. There was a normal birth and developmental history, but a reported history of epilepsy. An abnormal electroencephalogram was recorded and the intelligence quotient was 64. This individual was not available for examination but was reliably reported to have had no facial lesions. The diagnosis was mental retardation and epilepsy.

H-4: A 19 year old white male was born May 17, 1933, the twin of H-5. He was a behavioral problem, and was reported to have had cutaneous lesions, the nature of which could not be determined because of lack of cooperation. These lesions were reported to be of a transitory nature. The intelligence quotient was 55, and the diagnosis, mental retardation.

H-5: A white female, the twin of H-4, was born May 17, 1933, and died August 24, 1935, in status epilepticus in a Michigan mental institution. There was marked mental and developmental retardation. The diagnosis was severe mental retardation and epilepsy. The maternal grandfather was born August 22, 1856, and died in 1922 of reported heart attack or stroke. He could read and write but had had no formal schooling. There was no history of physical

or neurologic abnormalities. The maternal grandmother was born May 27, 1861, and was living at last report in 1944. She could read and write but had no formal schooling. She was reported to have been of at least average intelligence. There was no history of physical or neurologic abnormalities.

DISCUSSION

Since Hintz' original publication a number of case reports have been published purporting to show the coexistence of tuberous sclerosis and neurofibromatosis in the same individual. Carol and van Heusden,[6] who have reviewed all such cases reported prior to 1935, including Hintz', assert "that in no instance is adequate proof offered, either clinically or pathologically, for the coexistence of the two syndromes." Similarly, Borberg[7] rejects the cases reported by Petersen,[8] Dalsgaard-Nielsen,[9] Babonneix and coworkers,[10] Chargin,[11] and Skeer[12] for lack of histologic proof of the presence of neurofibromatosis.

More recently, Budenz[13] has reported a case described as tuberous sclerosis without epilepsy or mental retardation but with numerous skin lesions including peau de chagrin and colloidomas. Budenz asserts that these skin lesions may be identical with those of neurofibromatosis; however, five biopsies failed to disclose a single neurofibroma. The roentgenographic changes were not those typical of tuberous sclerosis. One is forced to conclude, therefore, that Budenz' diagnosis of tuberous sclerosis is based solely on cutaneous changes without the neurologic or roentgenographic changes found in tuberous sclerosis.

In view of the wide variation in what is clinically acceptable as tuberous sclerosis, a satisfactory resolution of the problem of the possible coexistence of these two syndromes seems dependent upon the description of the classic form of tuberous sclerosis and of neurofibromatosis in the same individual. Tuberous sclerosis, in the classic form, is recognized as a complex of signs consisting of adenoma sebaceum, mental retardation, and epilepsy. To this initial triad has been added subungual fibromatosis (Kothe[14]) and characteristic roentgenographic changes (Holt and Dickerson[15]). In the authors' estimation the only defensible diagnosis of tuberous sclerosis where clinical evidence of mental retardation or epilepsy is lacking is that diagnosis based upon pathologic or roentgenographic demonstration of tuberosclerotic cerebral changes. A diagnosis of classic neurofibromatosis, on the other hand, is dependent upon the histologic demonstration of multiple neurofibromas, since neither the pigmentary changes nor the other polymorphous peripheral and central abnormalities found in von Recklinghausen's disease are essential concomitants.

The proposita of this kindred (A-2) evinces all of the stigmata associated with classic tuberous sclerosis. Moreover, this patient exhibited pigmentary changes in excess of those observed among the other affected members of her kindred or among 49 nonrelated individuals with this disease seen during the course of the previously mentioned survey. These pigmentary changes were readily explicable only if the patient also had neurofibromatosis (Crowe and Schull[16]). Histologic examination of two of the violaceous tumors confirmed the presence of multiple neurofibromas.

The coexistence of these two syndromes in a single individual can be reconciled genetically with the thesis that they either are or are not variations of the same basic defect. However, any genetic hypothesis which attempts to account for these syndromes on the basis of the modification of a single gene, a necessary corollary to Hintz' argument, must admit the existence of intermediates between classic neurofibromatosis on one hand and classic tuberous sclerosis on the other. There was no evidence within this kindred or among 49 unrelated individuals with tuberous sclerosis that such intergrades existed. In view of the absence of such evidence the authors believe that the more logical genetic explanation is one which envisages two dominant genes. The existence of both syndromes in an individual when only one existed in the parents would then be accounted for by mutation, as suggested by Butterworth and Wilson.[17]

SUMMARY

A kindred is described in which six cases of classic tuberous sclerosis were distributed in a manner consistent with simple dominant inheritance. The coexistence of von Recklinghausen's neurofibromatosis and Bourneville-Pringle's tuberous sclerosis in one individual of this kindred is reported. It is suggested that mutation could readily account for such a finding.

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Adie's Syndrome and the Adler-Scheie Mecholyl Test

Bertram E. Sprofkin, M.D.

In 1931, Adie[1] reported a syndrome characterized by a tonic pupillary reaction and the absence of one or more tendon reflexes. He subsequently offered a rather elaborate classification of the condition.[2] In this classification he described a "complete form," consisting of the tonic pupil and absent reflexes, and an "incomplete form," which includes any of the following: a) only the tonic pupil, b) atypical phases of the tonic pupil, c) atypical phases of the tonic pupil with absent reflexes, or d) only absent reflexes. However, the validity of including patients with areflexia but normal pupils under this diagnostic rubric has not been generally acknowledged.[3,4]

The pupillary reaction now identified with Adie was first described independently by Strasburger[5] and Saenger[6] in 1902 and called by the latter the "myotonic pupil." A very slow, almost imperceptible, contraction to light and upon near vision, followed by a slower dilatation on removal of the stimulus, is the essential characteristic of this phenomenon. The reaction of the tonic pupil to light may be demonstrated more easily if the patient is placed in a dark room for as long as an hour before the test. Frequently the tonic contraction and dilatation are overlooked, and the pupil is regarded as nonreactive or "fixed." During near vision, sometimes after a delay of as long as five minutes, the abnormal pupil may contract slowly until it becomes smaller than the normal one. The tonic pupil is usually larger than its fellow and, in the majority of instances, is unilateral. In the celebrated case described by Markus, the affected pupil had become the smaller one when the patient was examined 27 years later by Weber.[7] The tonic pupil often varies in size during the day, a fact noted by Alajouanine and Morax,[8] Walsh,[9] and others.

Adie[10] and, later, Merritt and Moore[11] have emphasized that the Argyll Robertson pupil, as described by its discoverer, is small, constant in size, unaltered by light or shade, and usually bilateral. Upon near vision it contracts fully and promptly and dilates with equal speed when the stimulus is withdrawn. It dilates slowly and imperfectly to mydriatics. In Adie's emphatic words, the Argyll Robertson pupil "thus differs from the tonic pupil in every

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essential particular and can hardly be confused with it by anyone who is familiar with the characteristic features of both anomalies."

The tonic pupil is much more common in females than in males. Although the age of onset may be difficult to ascertain, this benign condition has been noted in patients of all ages. Schachter[12] reported a case in an eight year old child who was considered an imbecile. In discussing hereditary features, Walsh[9] quotes Dressler, who reported three sisters with tonic pupils. In seven of ten members of this family there were spasmodic alterations in the size of the pupil or hippus. Leeuwen,[13] in 1946, studied the hereditary background in five cases of tonic pupil and in another case in which the complete Adie's syndrome was exhibited. A total of 63 people were examined, but in no case could a "hereditary tonic pupil" be proved. In none of these families were there signs of any congenital affection of the nervous system.

Kennedy, Wortis, Reichard, and Fair[14] and Dynes[3] commented on the association of Adie's syndrome with emotional disturbances and cited cases indicating that the pupillary disorder is greater during periods of emotional stress.

In 1940, Adler and Scheie[15] reported on the response of the tonic pupil to weak solutions of Mecholyl chloride instilled in the conjunctival sac. In a series of 11 patients, every tonic pupil constricted with 2.5 per cent Mecholyl whereas the normal pupils were unaffected by the drug. In concentrations of less than 15 per cent, Mecholyl had no effect on the normal pupils of 48 subjects. The response of the tonic pupil to Mecholyl suggested to these workers that the neuromuscular mechanism of the pupil was sensitized to the compound, since it is known that sensitization to acetylcholine occurs in the parasympathetic nervous system if the terminal ganglion or any part of the postganglionic fiber is damaged. The normal reaction to adrenalin and cocaine was thought to eliminate the sympathetic supply of the iris as a site of the lesion.

Adler and Scheie then studied the sensitivity of the cat's pupil to Mecholyl following injury or destruction of the ciliary ganglion and its pre- or postganglionic fibers. They also observed the pupillary reactions in one patient whose ciliary ganglion had been removed during an operation for neurofibroma of the orbit, and in two others whose long ciliary nerves were presumably injured during electrocoagulation of a detached retina. In the experimental animals and in these patients they found that a permanent sensitivity of the pupil to Mecholyl develops if the ciliary ganglion or its postganglionic fibers are damaged. They concluded that the lesion in tonic pupils is situated in the postganglionic parasympathetic fibers themselves, anywhere from the ganglion up to the termination of the fibers, in the sphincter muscle of the iris. Furthermore, they determined that the lesion must represent only a partial denervation, since the pupils remain capable of reacting to all stimuli.

In a speculative paper on this subject in 1942, Leathart[16] also postulated that the lesion in the tonic pupil syndrome must be in the ciliary ganglion, where it causes an error in conduction between the pre- and postganglionic

fibers. He hypothecated that the loss of deep reflexes in this syndrome might be explained by a lesion in the sacral and lumbar segments of the cord in the intercalated fibers connecting the posterior root fibers with the anterior horn cells. After calling attention to Holmes' description of this entity in 1931 under the title of "partial iridoplegia," Leathart suggested that the term, "ciliary ganglion iridoplegia," might be better than "tonic pupil," since it indicates the site of the lesion. Wartenberg,[17] deploring the use of eponyms, pointed out that Weill and Reys had previously described this condition in 1926. He suggested "pseudotabetic pupillotonia" as a more physiologic name.

In 1948 Weekers[18] reported on the occurrence of tonic pupil as a rare complication following the retrobulbar injection of alcohol. The resulting pupil is characterized by semi-mydriasis, rigidity to light, and a tonic reaction on convergence. It also exhibits remarkable sensitivity to Mecholyl. He concluded that the occurrence of this therapeutic complication supports the contention that the tonic pupil is the result of a lesion of the parasympathetic iridoconstrictor fibers in the orbit below the level of the ciliary ganglion.

Although the studies of Adler and Scheie[15] and Scheie[19] on the pupillary reactions to Mecholyl are well known to ophthalmologists and have been verified by Dynes,[3] Walsh,[9] and others,[20,21] there is little reference in the neurologic literature to the usefulness of this knowledge. The applicability of the Mecholyl test is further illustrated by the following case reports.

CASE REPORTS

Case 1.—A 41 year old unmarried woman entered the hospital on April 5, 1953, for diagnostic study because her pupils were unequal. Anisocoria was first noted in December 1951 when she entered the hospital for a hysterectomy. Her complaints included giddiness, nervousness, numbness of hands and feet, increased fatigability, and headache. There was a long history of emotional lability. Gait, station, strength, and coordination were within normal limits. The knee and ankle jerks were absent bilaterally despite reinforcement. The plantar response was flexor. Sensation was entirely normal.

Except for the pupils, the cranial nerves showed no abnormality on examination. The diameter of the patient's right pupil was 5 mm. as compared with 3 mm. for the left. The right pupil was irregular and roughly oval in outline. There was no detectable reaction to light on the right, but a slow constriction of that pupil was observed on near vision. The left pupil reacted very slowly to light and upon near vision. After remaining in the dark for 15 minutes, both pupils dilated, but the right persisted as the larger.

The serologic test for syphilis had negative results in both the blood and cerebrospinal fluid, and the latter was normal in other respects as well. The general physical examination and the routine laboratory procedures were within normal limits.

Twenty minutes after the instillation of 2 drops of 2.5 per cent Mecholyl in each conjunctival sac, both pupils became greatly constricted. They dilated promptly when 10 per cent Neo-synephrin was dropped into each eye (figure 1). The normal pupils of a control were unaffected by this concentration of Mecholyl (figure 2).

The clinical diagnosis was: 1) mixed psychoneurosis and 2) Adie's syndrome.

Case 2.—A 56 year old housewife was admitted to the hospital on September 16, 1952, complaining of weakness of the left lower extremity. Her illness began about six months before admission when she experienced progressive instability of the left ankle and began to drag her left foot. At about the same time she became aware of muscle cramps involv-

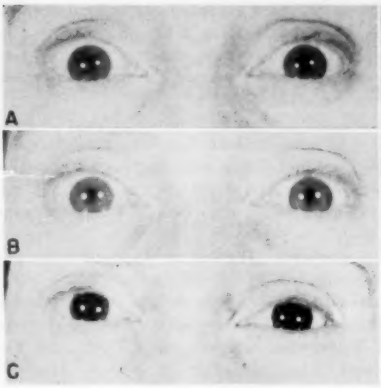

FIG. 1. (left) (Case 1). *A.* Patient with bilateral tonic pupils. Right pupil is larger and irregular. *B.* Miosis following instillation of 2.5 per cent Mecholyl. *C.* Normal response to mydriatic (10 per cent Neo-synephrin).

FIG. 2. (right). Control subject. Normal pupils are not constricted by the test solution of Mecholyl. *A.* Before medication. *B.* Twenty minutes after instillation of 2.5 per cent Mecholyl.

ing both legs and the left upper arm. Shortly before admission to the hospital she noted weakness of her left hand and observed occasional twitching movements of many muscles. She had been examined by a physician four weeks previously and was told that her pupils were unequal. There was no history of visual disturbances. She had been having "sick headaches" for 20 years.

On neurologic examination it was observed that the patient dragged the left foot in walking and exhibited little flexion of the left knee. There was slight circumduction at the hip. Fine shimmering fasciculations were evident in almost all her muscles, and there was occasional myoclonus. Her grasp was weak on the left, and the dorsiflexors of the left wrist exhibited considerable loss of strength. She had moderate diffuse weakness of the muscles of the left lower extremity. Wasting of the intrinsic muscles of the hand was pronounced on the left and minimal on the right. The dorsum of the left hand was guttered as a result of interosseous atrophy. There was bilateral absence of ankle and knee jerks, although the other deep reflexes were normal. The superficial abdominal reflexes were present and equal. The left plantar response was equivocal; the right was flexor.

Results of the sensory examination were normal. The left pupil measured 5 mm. in diameter and was larger than the right. Although the right pupil reacted briskly to all stimuli, the left reacted sluggishly to light and only after it had first been shielded from the light for a short while. It also responded slowly on near vision. There was moderate weakness of both sternomastoids and early lingual atrophy on the left. Speech and swallowing were not affected. The cerebrospinal fluid was under normal pressure. It contained 27 mg. of protein per 100 cc. and 3 white blood cells per cu. mm. The Kahn test of the blood and the cerebrospinal fluid Wassermann were negative.

When 2.5 per cent Mecholyl was dropped into each eye, the right pupil was unaffected, but the left became greatly constricted. During the subsequent few days of hospitalization it was noted that the left pupil varied considerably in size and at times was barely larger than the right.

The clinical diagnosis was: 1) amyotrophic lateral sclerosis and 2) Adie's syndrome.

Case 3.—A 35 year old machinist was admitted to the hospital on December 8, 1952, complaining of nervousness and intermittent headache. For several months he had been troubled by insomnia, nightmares, and inability to concentrate on his work. He drank heavily and smoked three packages of cigarettes daily. He had been in numerous fist fights,

and on one occasion, two years before admission, had been clubbed on the head until he became unconscious. About ten years before this hospitalization, while in the Army, he had been treated for one year with arsenicals and bismuth because of a positive blood test. There was no history of a primary lesion. Shortly before he entered the hospital a friend told him that one of his pupils was larger than the other.

The significant findings on neurologic examination were limited to the deep reflexes and the pupils. The right knee jerk and ankle jerk were obtained only after reinforcement. The other reflexes were normal. The left pupil measured 5 mm. in diameter and presented a slightly irregular outline, while the right was regular and 3 mm. in diameter. No significant reaction to light or on near vision was detected on the right, and the left pupil reacted very slowly to both stimuli. After a 40-minute period in a dark room, both pupils appeared equal and measured about 4 mm. in diameter. The left pupil again responded more promptly to stimuli and only a minimal reaction was observed on the right to either light or near vision. Results of sensory examination were entirely normal, as were roentgenograms of the skull and an electroencephalogram. The Kahn test of the blood was 3 plus on two occasions, but the cerebrospinal fluid Wassermann was negative. There were two white blood cells per cu. mm. of spinal fluid and 34 mg. of protein per 100 cc. Mecholyl instillation resulted in bilateral pupillary constriction.

The clinical diagnosis was: 1) late latent syphilis, adequately treated (irreversible serologic test), and 2) Adie's syndrome.

COMMENT

The problem presented by the tonic pupil is its differentiation from the Argyll Robertson pupil of neurosyphilis. When the complete Adie's syndrome is present and the deep reflexes are entirely or partly absent, a greater similarity to tabes dorsalis is presented. However, the semi-dilated tonic pupil, varying in size independently of the lighting, and reacting slowly on near vision and almost imperceptibly to light, should not readily be confused with the Argyll Robertson pupil. The latter is miotic and constant in size, reacts promptly to near vision, and is rigid to light and irregular in its response to mydriatics. The reaction to Mecholyl and the normal response to mydriatics of the tonic pupil constitute other distinguishing features.

The first case illustrates this differentiation and is one of the many instances in which this syndrome occurs in an emotionally labile woman. The third case presented more of a problem because here the pupillary abnormality appeared in a patient with a positive blood test and a history of antiluetic therapy. In each instance the Mecholyl test was a simple and helpful aid in differential diagnosis.

The history of alcoholism, cranial trauma, and headache in case 3 furnished an adequate background for a diagnosis of subdural hematoma. The semi-dilated pupil could also have been confused with the fixed dilated pupil resulting from third nerve compression by a displaced cerebral hemisphere. The absence of other neurologic findings, the character of the pupillary reactions, and the laboratory findings facilitated diagnosis.

A survey of the relevant literature would indicate that case 2 is a unique example of the occurrence of a tonic pupil in a patient with amyotrophic lateral sclerosis. The initial history of progressive left-sided weakness in this patient with a unilateral dilated pupil raised the immediate suspicion of an

expanding intracranial lesion, but the facts of the history and the findings on examination indicated that the anomalous pupil was unrelated to the other neurologic signs. This patient showed no muscle atrophy of the lower extremities, although this may have been concealed by adiposity. One can only conjecture as to whether the absence of knee and ankle jerks was associated with the tonic pupil or represented a manifestation of the amyotrophy. The latter explanation seems less likely.

A brother of the patient in case 1 was examined, and his pupils were found to be normal. It was not possible to investigate further the familial aspects of the anomaly.

Although it is not common for patients with this syndrome to complain of ocular disturbances, Sykowski[20] has suggested the use of weak solutions of Mecholyl or pilocarpine to control photophobia resulting from pupillary dilatation.

SUMMARY

Three cases of Adie's syndrome or tonic pupil occurring in patients with psychoneurosis, amyotrophic lateral sclerosis, and latent syphilis are presented.

The usefulness of the Adler-Scheie Mecholyl test in the diagnosis of Adie's syndrome is demonstrated.

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Cerebrospinal Fluid Pressure Adjustment to Change in Body Position

John Fay, M.S., and Paul Settlage, Ph.D., M.D.

WEED[1] has demonstrated that there is a marked and sudden change in cerebrospinal fluid pressure in animals when the body is changed from the horizontal position to the vertical head-up or head-down position. On shift to the head-up position cisternal pressure drops, whereas the lumbar pressure increases. The reverse is true in shift to the head-down position. Loman, Myerson, and Goldman[2] have confirmed these results in man.

The above authors were concerned primarily with the immediate consequence of shift in body position. The present study is concerned with the adaptive changes which occur in monkeys and cats when a given body position is maintained for a period of time.

METHOD

Four Macaca mulatta monkeys and four cats were used as experimental subjects. All were adults. One animal of each species was subjected to three successive experiments at intervals of not less than two weeks. The remaining three animals of each group were used in one experiment each.

Cerebrospinal fluid pressure responses were observed for three degrees of inclination of the body axis in each experiment. The three positions were: horizontal, 30-degree inclination with head down, and 30-degree inclination with head up. Each position was maintained for a standard length of time and the conditions followed each other in a standard succession as follows: 1) 0-120 minutes – horizontal (control period); 2) 120-240 minutes – 30-degree inclination – head down; 3) 240-300 minutes – horizontal; 4) 300-420 minutes – 30-degree inclination – head up; 5) 420-480 minutes – horizontal.

The entire apparatus for holding the animal and measuring pressure was mounted on a table which could be tilted to the desired degree. The animal's head was held rigidly in a special ear bar type holder and the posterior portions of the body were anchored by tying the tail to one end of the table with

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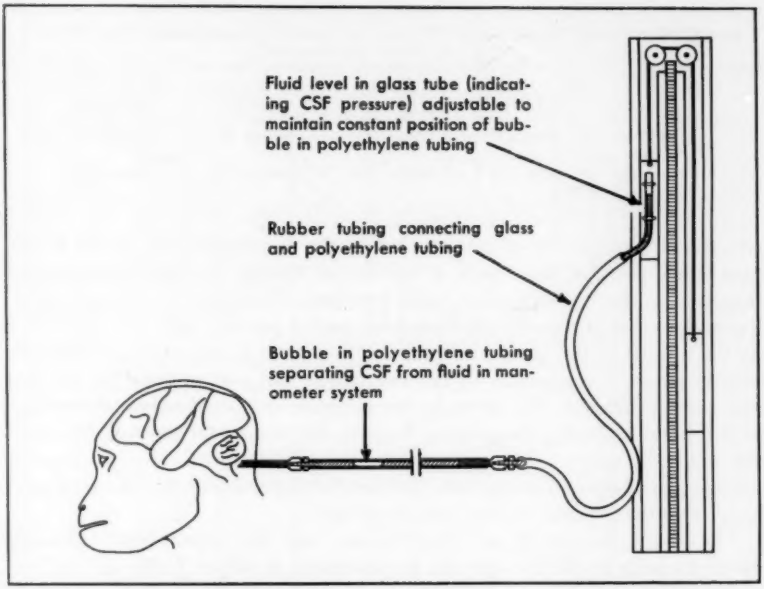

Fluid level in glass tube (indicating CSF pressure) adjustable to maintain constant position of bubble in polyethylene tubing
Rubber tubing connecting glass and polyethylene tubing
Bubble in polyethylene tubing separating CSF from fluid in manometer system

FIG. 1. A diagram of the bubble manometer used in measurement of cerebrospinal fluid pressure.

liberal use of adhesive tape and twine. The degree of tension on the tail was such as to prevent any significant degree of shifting of the body and spine when the table was tilted. Animals were always in a prone position.

All pressure measurements were made in the cisterna magna using a bubble manometer as diagrammed in figure 1. This type of manometer made it possible to measure pressure changes without permitting passage of fluid into or out of the animal's cistern. It was attached to the tilting platform in such a manner that it could be kept in a vertical position regardless of the inclination of the animal's body axis.

The anesthetic agent was Nembutal. Anesthesia was maintained by intramuscular administration as often as was indicated by observable response to mechanical stimulation of the ear, eyelids, or toe pads.

Pressure measurements were recorded at 15-minute intervals except during periods immediately following position change, when recordings were made as often as once a minute.

RESULTS

The trend of pressure change following shift in inclination of body axis was remarkably constant in all animals of both species (figures 2, 3, 4, and 5). The change from horizontal to head-down position resulted in an immediate and sharp increase in pressure, equaling a mean magnitude of 5.6 cm. in the

TABLE 1
MEAN PRESSURE CHANGE IN CENTIMETERS OF WATER IMMEDIATELY FOLLOWING SHIFT IN BODY INCLINATION

	Horizontal to Head Down	*Head Down to Horizontal*	*Horizontal to Head Up*	*Head Up to Horizontal*
Cats N = 6	plus 5.6	minus 5.0	minus 4.8	plus 4.7
Monkeys N = 6	plus 3.9	minus 3.8	minus 3.6	plus 4.1

cats and 3.9 cm. in the monkeys. During the succeeding two hours in the head-down position there was a continuous though negatively-accelerated decrease in the cerebrospinal fluid pressure, returning to a level which approached that of the original horizontal control period (table 1). On returning the animal to the horizontal position, there was a sharp drop in pressure roughly equal in magnitude to the rise which had occurred on the original shift from horizontal. This brought the pressure to a level below that of the control period. During the ensuing hour in the horizontal position the pressure gradually rose until it approximated the original level. The two ensuing positions, head-up and horizontal, produced changes which for practical purposes were the reverse of those just described.

The mean magnitudes of the changes and the adjustments following change in each of the two species are indicated in tables 1 and 2.

In summarizing the results, it may be stated that the cerebrospinal fluid pressure changes ensuing immediately on a change of 30 degrees in body inclination ranged from 2.8 to 5.6 cm. (mean 3.9) in monkeys, and from 4.7 to 6.7 cm. (mean 5.6) in cats. Following each instance of change in body inclination, cerebrospinal fluid pressure as measured in the cisterna magna, adjusted toward the original control level. The degree of adjustment following a change of 30 degrees in body inclination ranged from 0.9 to 3.4 cm. (mean 2.2) in monkeys, and from 1.4 to 6.7 cm. (mean 3.3) in cats.

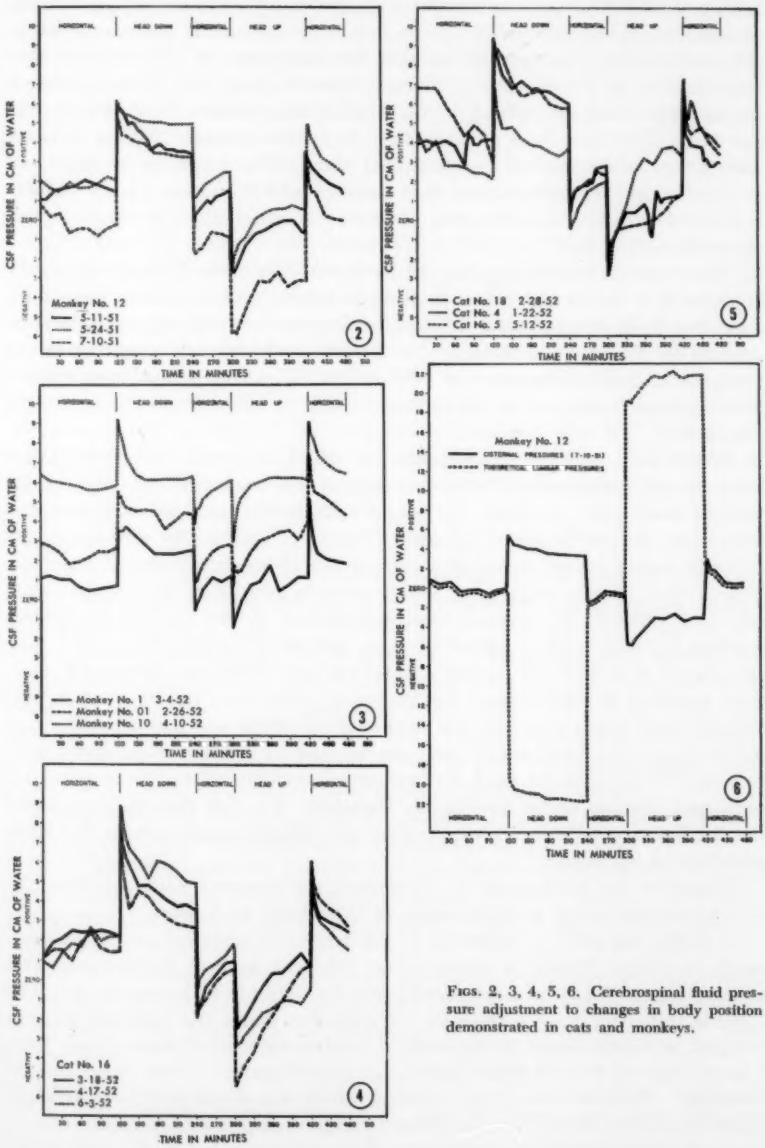
DISCUSSION

The mechanism producing cerebrospinal fluid pressure adjustments which have been demonstrated in monkeys and cats remains to be elucidated in

TABLE 2
MEAN PRESSURE ADJUSTMENT IN CENTIMETERS OF WATER DURING EACH SUCCESSIVE CONDITION OF BODY INCLINATION

	Head Down (120 min.)	*Horizontal (60 min.)*	*Head Up (120 min.)*	*Horizontal (60 min.)*
Cats N = 6	minus 3.7	plus 2.3	plus 4.3	minus 3.0
Monkeys N = 6	minus 1.9	plus 1.7	plus 2.7	minus 2.7

The probability that these values were due to chance was estimated by applying the "t" test[3] to the combined data for both groups of animals. The probability that the pressure changes occurring in the head down position were due to chance is less than 5 in 100. For the other three conditions the probability is less than 1 in 100.



FIGS. 2, 3, 4, 5, 6. Cerebrospinal fluid pressure adjustment to changes in body position demonstrated in cats and monkeys.

further studies. One postulate that has been developed in an approach to the problem of mechanism concerns the cerebrospinal-venous pressure relationship and is based on the premise that the absorption of cerebrospinal fluid is a function of the pressure difference between these two fluid systems. It is postulated that on shifting to the head-down position there is a greater rise in cerebrospinal fluid pressure than in venous pressure, with a resulting increase in absorption of cerebrospinal fluid. This produces a negatively accelerated fall in cerebrospinal fluid pressure which continues until stability is reached, at which time the rate of formation equals the rate of absorption of cerebrospinal fluid.

The pressure relationships would be reversed in a condition in which the adjustment is in the direction of rising cisternal pressure. There would be, according to this postulate, a decrease or increase in cerebrospinal volume to account for the pressure changes. The fact that adjustments occurring in one condition of body inclination are reflected in the pressure developed when a new position is adopted is interpreted as due to the volume change which occurred.

Weed[1] has reported experiments in which he measured the relation between the cerebrospinal fluid and sagittal sinus pressures in dogs in the vertical head-down position. He found that the venous pressure increases more than the cerebrospinal pressure. This is, of course, the direct opposite of what would be predicted in terms of the above postulate. The authors believe that Weed's findings do not necessarily invalidate the theory which has been offered. His animals were maintained in the vertical head-down position for only a short period of time, and in all probability would have succumbed if maintained in that posture for any substantial period. Of three dogs tested in this laboratory, the 30-degree head-down position led to fatal subarachnoid hemorrhage in one. Undoubtedly there are species differences in the ability to adjust, and it may also be that the vertical head-down position would prove to be fatal to any animal maintained in this position for prolonged periods under anesthesia. Therefore, it is felt that findings under the conditions of Weed's experiment are not directly applicable in the interpretation of our results.

Whatever the mechanism of adjustment, the reported findings allow several inferences which warrant comment. These are as follows:

1. Following shift in inclination of the body axis, cisternal pressure always tends to return toward a mean value, whereas lumbar pressure deviates widely. Figure 6 has been prepared using the formula of Loman et al.[2] The formula stated by these authors is: "The lumbar minus the cisternal pressure is equal or nearly equal to the vertical lumbar-cisternal distance, thus, from a knowledge of two of these factors, an approximation of the third can be obtained." With the aid of this formula, which was developed from data obtained by making simultaneous cisternal and lumbar pressure measurements in human subjects, the lumbar pressure values corresponding to the empirically determined cisternal values in monkey number 12 were calculated. It is clear,

from examination of this figure, that the lumbar values in the head-up and head-down position deviated from the mean of the horizontal pressures exactly as far as the cisternal pressures returned toward it. In other words, on assuming the head-down position, cisternal pressure shows a fall following the initial rise, whereas lumbar pressure initially falls only to fall still further as the position is maintained.

2. The adjustment mechanism, if it operated in the unanesthetized human subject, would be expected to have an unfavorable effect on the validity of clinical measurement of lumbar pressure, unless the position of the subjects is controlled. The results which have been presented make it clear that different pressure values would be obtained from a subject if measurement were made immediately after the shift from a sitting position to the lateral decubitus, or after the patient had been in the lateral decubitus for a given period of time. The difference would be expected to be highly significant, in view of the fact that a 30-degree shift in body axis in the short-spined laboratory animals resulted in adjustments of 20 to 40 mm. of water. Stated otherwise, a high pressure value obtained in a subject who had been in the decubitus position for an hour or two prior to pressure measurement would be more significant than a similar value obtained shortly after change from the upright to the horizontal posture.

SUMMARY

1. The effect of prolonged periods of change in inclination of body axis upon cerebrospinal fluid pressure, as recorded in the cisterna magna, were studied.

2. On tilting the animal (cat or monkey) to the head-down position, the cerebrospinal fluid pressure immediately rose and then gradually returned toward the normal. On returning to the horizontal position following the head-down period, the cerebrospinal fluid pressure fell below the original control level and gradually returned to the normal. The reverse effects were noted for the head-up and the succeeding horizontal positions.

3. A mechanism for the adjustive process, involving the cerebrospinal fluid-venous pressure relationship, is suggested.

4. A theoretical curve is presented for the lumbar pressures which would occur concomitantly with the observed cisternal pressure values. The lumbar pressure tends to deviate from a mean value as far as the cisternal pressure returns toward this value.

5. A mechanism of adjustment such as seen in laboratory animals would, if demonstrable in the conscious human subject, prescribe an important set of conditions necessary for obtaining reliable measurements of lumbar pressure.

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PEDIATRIC NEUROLOGY

This new department has been instituted to give more specific attention to the many neurologic diseases and conditions occurring among children.

DOUGLAS N. BUCHANAN, M.D., *Section Editor*

Tumors Arising Within the Spinal Canal in Children

Alexander T. Ross, M.D., and
Orville T. Bailey, M.D.

TUMORS of the spinal cord in infancy and childhood were long regarded as rarities and the literature on the subject consisted of isolated case reports. Stookey[1] in 1928 reviewed eight instances, though only two were primary tumors of the spinal cord. With the impetus of this publication, larger series were reported, notably those of Hamby[2] in 1935 and Ingraham[3] in 1938. The comparative frequency and clinical importance of these tumors were thus established. Yet as recently as 1947, Krabbe,[4] whose experience is very large, stated that he had seen only six instances of spinal cord tumors in children. Thus some question of incidence and differential diagnosis still prevails.

It is the purpose of this paper to discuss 13 tumors of the spinal cord in infants and children. An attempt has been made to discover the frequency of these lesions relative to spinal cord tumors in adults in a medical center which includes teaching hospitals, a large city hospital, and a hospital devoted to private patients. In this it differs from such reports as Hamby's[2] and Ingraham's,[3] which were based on a highly selected material in services devoted to pediatric neurosurgery. This paper also seeks to point out diagnostic and pathologic problems which occur in isolating these tumors from completely unselected material.

Only patients with neoplasms originating within the spinal cord or its meninges are included in this study. Metastatic lesions and tumors originating in or invading the extradural space have been specifically excluded. All tumors without satisfactory histologic material have also been excluded, as well as lesions not specifically known to be neoplastic, such as hydromyelia and syringomyelia.

MATERIALS AND INCIDENCE

The records of all patients with tumors of the spinal cord were reviewed

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from the Indiana University Medical Center, 1934 to 1953; from the Indianapolis General Hospital, 1938 to 1953; and from the Methodist Hospital (Indianapolis), 1936 to 1953. Those not fulfilling the criteria stated previously were excluded. A total of 63 patients were selected, and their histories, operative and postmortem findings were reviewed and analyzed.

Material obtained at operation or autopsy was re-examined in connection with the clinical data, and clinicopathologic correlations were made when possible. In every case material was available for this study, permitting a uniform nomenclature and interpretation regardless of the source.

Of the 63 patients available from the three hospitals, 13 were under the age of 16 years and 50 were older; thus 20 per cent of all tumors of the spinal cord occurred under the age of 16 years. This is in fair agreement with the old statistics of Schlesinger,[5] who found that 24 per cent of a series of 251 tumors of the spinal cord were in patients under 15 years. It is quite different from the percentages cited by many surveys from that of Stookey[1] to that of Krabbe[4] or the more restricted one of Webb, Craig and Kernohan.[6] It is felt that the material reported here is more nearly a representative cross-section than that of a highly specialized neurosurgical service, especially one in which many or most patients are referred from distant areas. No explanation can be offered for the low incidence reported by Krabbe[4] or for the general feeling of European neurosurgeons that tumors of the spinal cord are very rare under the age of 15 years.

As to the relative incidence of intramedullary and extramedullary tumors in the entire series of 63 patients, 36 were intramedullary (57 per cent) and 27 were extramedullary (43 per cent). Of the intramedullary tumors, 29 occurred in adults and seven in children. Twenty-one of the extramedullary tumors were in adults and six in children. The incidence of the various histologic types is shown in table 1.

TABLE 1

TUMORS ARISING WITHIN THE SPINAL CANAL

	Adults	*Children*
Astrocytoma	8	4
Lipoma	1	1
Ependymoma	9	1
Hemangioma	7	1
Glioblastoma multiforme	4	0
Teratoma	3	2
Fibrosarcoma	0	1
Neurinoma	7	1
Neurofibrosarcoma	0	1
Meningioma	11	1
	50	13

CLINICAL FEATURES

The prime requisite for diagnosis of a spinal cord tumor is suspicion of its existence. This should be aroused by a history of progressive impairment of neuromuscular function, although when symptoms develop rapidly it is quite likely that an inflammatory process will first be suggested. In such instances the development of increasing symptoms and signs should lead to the suspicion of tumor. The precise symptomatology depends upon its location, extent, relationships to adjacent structures, rate of growth, and histologic type. It includes pain, weakness, atrophy, spasticity, alteration in reflexes, and sphincter disturbances. Examination of the cerebrospinal fluid, radiographic and, if indicated, myelographic studies will disclose the correct diagnosis in a high proportion of cases.

The importance of realizing that spinal cord tumors can occur in children is illustrated in the present series of 13 cases,

TABLE 2
SUMMARY OF CASES OF SPINAL CORD TUMOR IN 13 CHILDREN

Case	*Age at admission*	*Admission diagnosis*	*Final diagnosis*	*Course*
1	5 years	Postpolio	Conus astrocytoma	4 years postoperative: residual paraparesis
2	3½ years	Possible brain tumor	Cervical astrocytoma	2½ years postoperative: residual paraparesis
3	3 years	Postpolio	Cervical astrocytoma	Died 1 day postoperatively
4	9 years	Spondylolisthesis	Th-L-S astrocytoma	16 years postoperative: residual paraparesis
5	10 years	Cerebral palsy	Lumbar lipoma	2 years postoperative: residual paraparesis
6	2½ years	Possible Pott's disease	Conus ependymoma	2 years postoperative: residual paraparesis
7	10 years	Landry's paralysis	Lumbar hemangioblastoma	Died 6 months postoperatively
8	2 years	Possible left brain lesion	Thoracic cystic teratoid	8 years postoperative: complete recovery
9	10 months	Meningomyelocele	Cervical teratoma	Died 1 day postoperatively
10	15 years	Cord tumor	Thoracic fibrosarcoma	Died several months postoperatively
11	15 years	Postpolio	Neurinoma C8	Complete recovery
12	15 years	Rheumatoid arthritis	Cauda neurofibrosarcoma	Died 5 months postoperatively
13	14 years	Cord tumor	Cauda meningioma	6 years postoperative: residual paraparesis; enlarging sacral tumor

for in only two was the condition suspected on admission. The other admission diagnoses included residua of poliomyelitis, brain tumor, cerebral palsy, Landry's paralysis, Pott's disease, spondylolisthesis, rheumatoid arthritis, and meningomyelocele (table 2).

It is particularly important that children with spinal cord tumors do not receive the permanent diagnosis of postpoliomyelitic syndrome. They may have operations to correct deformities or receive long courses of physical therapy while the tumor is doing more and more irreparable harm to nervous tissues. This can be avoided by critical study of all patients with paralysis who have no clear history of typical acute poliomyelitis. The paralysis of poliomyelitis is stationary or improves, but that caused by a spinal cord tumor is progressive (see cases 1 and 4, table 2). Evidence of progressive neural dysfunction, localizing signs of spinal cord involvement, and pathologic findings in the cerebrospinal fluid should suggest the proper diagnosis.

In this series consisting of seven intramedullary and six extramedullary tumors, the predominant symptom in the former was weakness of one or more extremities; in the latter it was pain in the distribution of a nerve root aggravated by movement of the spine, by jarring, or by coughing.

Intramedullary lesions usually produced bilateral and generally symmet-

rical atrophy, hypotonia, and hyporeflexia of the muscles supplied by the affected segments. The results of sensory examination were not always reliable in these children, but when deficits were found they were usually fairly symmetrical or extensive. When the cervical enlargement was the site of the tumor, innervation of the arms and diaphragm were interfered with and there was compression of the motor tracts to the sphincters and the legs. Tumors in the lumbosacral region affected the sphincters and legs quite symmetrically, producing atrophy, weakness, and hyporeflexia in four instances, and spasticity in one.

Extramedullarly tumors, on the other hand, usually began unilaterally with pain over a root distribution, and in the early stages of expansion gave rise to asymmetrical signs. Those in the cervical and thoracic regions caused compression of the descending motor fibers resulting in sphincter disturbances, hyperreflexia, and Babinski's sign. Tumors of the cauda equina began with unilateral pain, but rapidly progressed to symmetrical atrophic paralysis and areflexia. Thus, from the history and findings one can presumably differentiate intramedullary from extramedullary tumors, the former being characterized by weakness and symmetrical involvement of structures, the latter by an onset with unilateral pain and, at least during a phase of development, asymmetrical compression of structures.

Examination of the cerebrospinal fluid and its dynamics cannot be relied upon to differentiate the two groups of tumors. It was xanthochromic in four cases of intramedullary tumor and in three of extramedullary tumor. Jugular compression disclosed a block in five of the former and in four of the latter. Myelography proved valuable in determining the site of obstruction in two instances – one astrocytoma and one lipoma – in which no block was demonstrated on jugular compression. Quantitative protein values ranged from 344 mg. per cent to 5,700 mg. per cent in five of the seven cases of intramedullary tumor. In the patient with a lipoma the protein content was normal, and in one, no estimation was recorded. In cases of extramedullary tumor, the protein content varied from 120 mg. per cent to 10,000 mg. per cent. In general, the protein levels were higher in the intramedullary group.

Roentgenographic abnormalities were observed in four of the seven cases of intramedullary tumors and in two patients with extramedullary lesions. These consisted of widening of the neural canal, erosion of a pedicle, or developmental defects, which were of little differentiating value.

The response to operation depends upon the site, histologic type, and structures involved by the tumors. Two patients with sacral and one with cervical astrocytoma, one with ependymoma, and one with lipoma are living, though paraparetic, two to 16 years after decompression of the cord with partial removal of the tumor. One patient with high cervical astrocytoma died one day after operation. One with hemangioblastoma died six months after surgery. In the extramedullary group, one patient with a cystic teratoid tumor and one with neurinoma made complete recoveries. One with an enlarging, destructive meningioma over the sacrum is bedfast and paraplegic. One with a high cervical teratoma died one day after operation. One with fibrosarcoma and one with neurofibrosarcoma died within five months of operation. In general, if an extramedullary tumor is accessible and nonmalignant the prognosis is excellent. Decompression of intramedullary tumors permits a paraplegic existence for a considerable number of years. That this need not be entirely dreary is illustrated by case 4 which is discussed in detail below.

PATHOLOGIC CONSIDERATIONS

Each specimen of the pathologic material from patients in this series was restudied for classification by uniform criteria, and to determine whether any additional information could be secured in the light of the follow-up studies. The diagnoses are listed in table 2.

The gliomas corresponded histologically to the well-known descriptions of these tumors, but contributed no new facts regarding them. This was also true in instances of teratoma, meningioma, hemangioblastoma, and neurinoma.

The three remaining tumors do, however, require special comment. The lipoma (case 5) was within the substance of the spinal cord, appearing as a true neoplasm and not an extension of a tissue malformation. It is interesting to speculate whether the lipoma represented a tumor of cells misplaced some time after gastrulation, as suggested by Vonderahe and Niemer.[7] Since it lay well within the substance of the spinal cord, it did not occupy the usual position of an intraspinal teratoma.[8] It is felt that a sharp distinction should be made between true lipomas and the masses of fat, often designated as "lipoma," which are an overgrowth of fat tissue as part of failure of embryonic organization in the region of the spinal column, and are associated with spina bifida, overgrowth of blood vessels, and other tissue anomalies in the area.

The fibrosarcoma in case 10 was an extremely rapidly growing neoplasm which formed a collar about the spinal cord and apparently originated in the dura. There was another deposit of fibrosarcoma adjacent to the spinous process of C7 and a shadow in the right lung was observed by roentgenogram. One may therefore raise the question as to whether the extraspinal fibrosarcoma was primary and the intraspinal, a metastasis. We feel, however, that the histologic similarity to that seen in intracranial fibrosarcoma (Bailey and Ingraham[9]) and an initial history of spinal cord involvement indicate that the tumor in the spinal dura was the primary one. It might be noted in passing that case 2 in Bailey and Ingraham's[9] paper later came to autopsy; there were several extracranial metastases.

There is little question that the tumor in case 12 was derived from a sheath of the intraspinal portion of a spinal nerve (figure 1). Its designation as neurofibrosarcoma rather than neurinoma might be questioned. The tumor was somewhat more cellular than the usual spinal neurinoma, but tumor giant cells were not a prominent feature. However, mitoses were extremely numerous, sometimes as many as ten per high power field. It was this feature which did not seem consistent with a diagnosis of neurinoma and led to placing the case in the category of neurofibrosarcoma.

The large variety of diagnoses in a series of tumors is consistent with the finding of many authors that the spread of histologic types among intraspinal tumors in children is greater than in intraspinal tumors in adults, if the sizes of the series are comparable.

CASE REPORTS

Case 1.—Weakness of left foot in a boy of five years, regarded as having postpoliomyelitic syndrome until definite progression of signs under treatment. Laminectomy: intramedullary tumor. Histology: astrocytoma. Alive with residual weakness of legs four years later.

A five year old white boy was admitted to the Indianapolis General Hospital on June 21, 1949 because of weakness and clumsiness of the left foot. This had begun seven months previously and was becoming progressively more noticeable. He also complained of abdominal pain when he coughed or sneezed. Although there was no history of poliomyelitis, he was considered to have residua of this disease and was treated on an outpatient basis with exercise and braces. His unsatisfactory response to treatment prompted hospital admission. A few days after this he developed constipation and in-

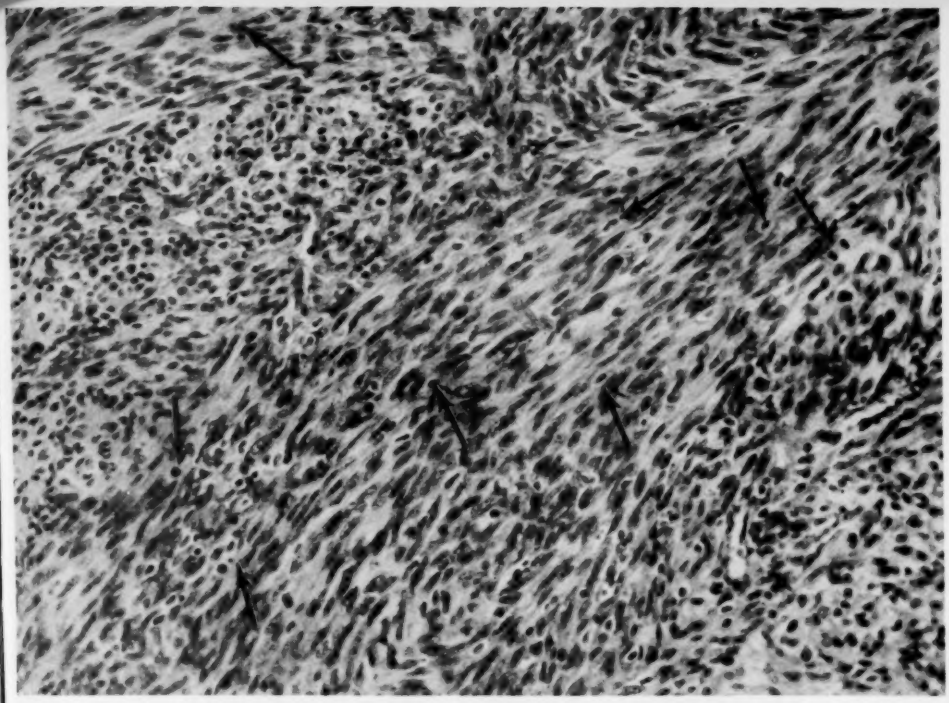

FIG. 1. Neurofibrosarcoma in case 12 (table 2). Note the interlacing bundles of cells and palisading of nuclei. There are over 20 mitoses in this field, some of which are indicated by arrows. Hematoxylin and eosin stain.

termittent urinary retention and dribbling.

The pertinent positive findings included hypotonia and weakness of the left thigh, leg, and foot group of muscles; left pes cavus; absent left cremasteric reflex; absent patellar and achilles reflexes bilaterally; hypalgesia and hypesthesia below Th12 on the left; perianal analgesia on the left and hypalgesia on the right; absent anal reflex; and loss of vibration sensibility at the left ankle.

The cerebrospinal fluid was xanthochromic and had an opening pressure of 85 mm. There was a prompt rise and fall on jugular compression, but after removal of 6 cc. the pressure was reduced to 30 mm. There were 5 lymphocytes, a 4 plus Pandy reaction, and a protein determination of 4,500 mg. per cent.

Roentgenograms disclosed a scoliosis to the right at L1 and a questionable widening of the pedicles in the lower dorsal area. Pantopaque myelography revealed a block at L1.

Laminectomy from Th10 to L1 exposed a neoplastic mass fused with the pia-arachnoid and compressing the conus medullaris and cauda equina. On the dorsum of the neoplasm were three cystic areas which did not communicate with one another and which, on incision, released syrupy, bloody fluid. He was given postoperative roentgen irradiation.

Histologically, the tumor was a glioma of low cellularity. The cell type was a mature astrocyte with numerous processes. No immature cells were seen and no mitoses were present. The astrocytes were somewhat separated from one another by edema. The relatively few blood vessels showed no proliferative changes. The histologic diagnosis was astrocytoma.

During the ensuing four years the patient required orthopedic supervision for a severe kyphoscoliosis. Examination in January 1953 revealed diffuse hypotonia, atrophy and weakness of both lower extremities, and impaired position sense of the toes. The saddle analgesia had disappeared and he had regained sphincter control. He was able to shuffle about.

Case 4. Inability to walk in a girl of nine years. Examination: flaccid paralysis of both lower extremities; pyramidal tract signs. Laminectomy: intramedullary tumor at Th7 and 8. Histology: astrocytoma. Remains paraplegic after 16 years but earns own living.

A 9 year old white girl was first admitted

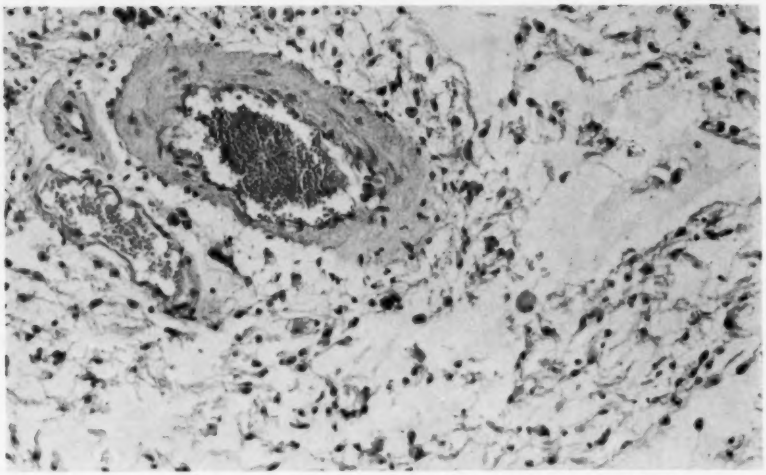

FIG. 2. Astrocytoma of spinal cord in case 4 (table 2). Hematoxylin and eosin stain.

to the Indiana University Medical Center on June 24, 1936 because of pain in the back and inability to walk, which started three months previously as difficulty in handling her legs. The examination was very inadequate, the only pertinent notations being tenderness over the lumbosacral spine, spondylolisthesis, and scoliosis. She was given a back brace and discharged. Five months later she was readmitted because of frequency of urination and prickling sensations in the right foot and leg. There was no pain or incontinence.

The pertinent positive findings included a left lumbar and right thoracic scoliosis; flaccid paralysis of the thighs, legs, and feet bilaterally; absence of abdominal and patellar reflexes on both sides; absent right achilles reflex; bilateral Babinski sign; left ankle clonus; hypesthesia below L1 on the right; diminution of position and vibration sensibilities in the right foot; and preservation of superficial pain sense.

The cerebrospinal fluid was xanthochromic, showed a complete block on jugular compression, contained no cells, and had a protein content of 3,324 mg. per cent.

Roentgenograms disclosed scoliosis. Lipiodal instilled cisternally revealed a block at Th3, while a lumbar myelogram indicated an obstruction at L2.

A laminectomy was done removing the arches of Th10, 11, and 12. The spinal cord was diffusely enlarged and the posterior spinal veins were distended and tortuous. The tumor did not appear upon the surface of the cord at this level so the arches of Th9, 8, and 7 were removed. Beneath those of Th7 and 8 the tumor could be seen extending to the posterior surface. No fluid could be aspirated. A longitudinal incision was made bloodlessly into the tumor. It was found to be moderately soft, grayish, and avascular suggesting a glioma. It extended superiorly but because of its intramedullary nature and extent it was deemed futile to attempt to expose it completely. Hemostasis was effected; the dura was left wide open and the wound closed in layers.

Histologically, the tumor was composed of irregularly distributed astrocytes in a loose textured arrangement. The astrocytes were mature and no mitoses or areas of dense cellularity were found. Some of the moderately numerous blood vessels had a thick collagenous band beneath the endothelium but there was no evidence of atypical endothelial or adventitial proliferation (figure 2). Diagnosis was astrocytoma.

This patient has remained paraplegic. Her legs are atrophic and fixed in flexion contractures. She has a severe kyphoscoliosis and is subject to recurrent urinary tract infections and calculi. She has been con-

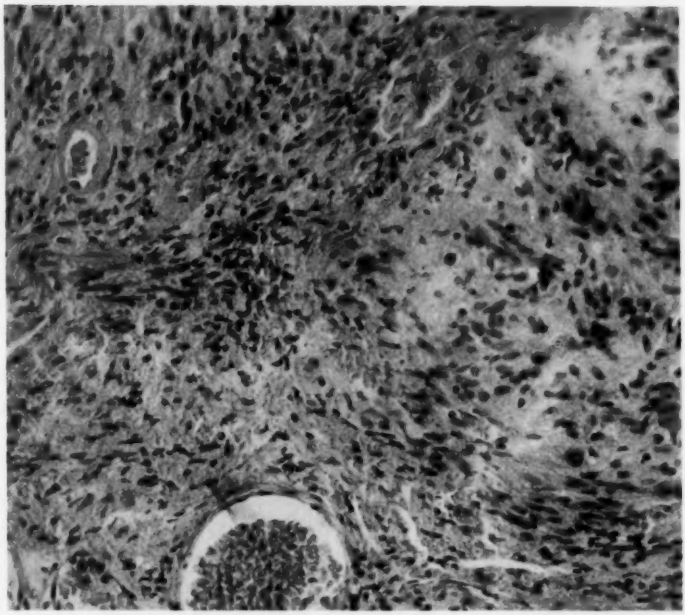

FIG. 3. Neurinoma of intraspinal portion of a spinal nerve in case 11 (table 2). Hematoxylin and eosin stain.

fined to her wheel chair for the past 16 years. Despite these handicaps she is remarkably well-adjusted, has completed a college course, written several articles for national magazines, works as a part-time stenographer, and expresses the view that "for a person given six months to live" she has done rather well.

Case 11.—A 15 year old boy with pain in right shoulder and arm. Postpoliomyelitic syndrome suspected. Laminectomy because of pyramidal tract signs revealed extramedullary tumor arising from C8 nerve root. Histology: neurinoma. Alive without residua 15 years later.

A 15 year old white boy was admitted to the Indiana University Medical Center on September 21, 1938 because of pain in the right shoulder and arm. Three years previously he had begun to have intermittent pain in the right shoulder radiating down the arm. This became more constant during the six weeks before admission and was associated with drawing of his head to the right. He was suspected of having postpoliomyelitic syndrome.

Examination disclosed limitation of neck motion with muscle spasm; obliteration of cervical lordosis; atrophy of the right biceps, triceps, and inner forearm muscles; reduction of the right biceps and triceps reflexes; hyperactivity of the right patellar reflex with transient ankle clonus; and Babinski sign. There were no sensory abnormalities.

The cerebrospinal fluid was clear; there was no block and no cells; and the protein content was 160 mg. per cent.

Operation exposed an extramedullary tumor anterior and to the right of the spinal cord at the level of C7 vertebra. It was below the arachnoid and apparently arose from the root of C8 on the right. It was about 25 mm. in diameter, reddish-brown, had a thin capsule, and derived its blood supply from one of the posterior spinal arteries. It had flattened the cord slightly from before backward. The C8 root was severed centrally and distally to the tumor, which was then delivered intact.

On histologic examination, the moderately cellular tumor was composed of loose, interlacing bundles of elongated cells. There were no mitoses and no areas of increased cellularity (figure 3). In a few areas, tissue containing fat-filled cells was present. The tumor was rather vascular. There were a few regions of dense fibrosis. The histologic diagnosis was neurinoma.

The patient was completely asymptomatic a month after the operation and has remained so for 15 years.

SUMMARY

Sixty-three tumors of the spinal cord and its coverings were found in a survey embracing material from a teaching medical center, a city hospital, and a large private hospital. Thirteen of the 63 tumors (20 per cent) occurred in children under 16 years.

Of the 13 spinal cord tumors in children, seven were intramedullary and six extramedullary. Clinically, the intramedullary tumors were usually characterized by painless symmetrical involvement of the spinal cord, whereas the extramedullary tumors usually began with radicular pain and unilateral signs. Examination of the cerebrospinal fluid could not be relied upon as a feature differentiating the two groups. However, the elevation of cerebrospinal fluid protein was of considerable diagnostic value in suggesting the presence of a spinal cord tumor since it was elevated in all but one.

The importance of searching for spinal cord tumor in progressive neural dysfunction in childhood is illustrated by the fact that in only two of the 13 proved instances was this diagnosis entertained originally. On three occasions the admission diagnosis was postpoliomyelitic syndrome. In this group the possibility of a spinal cord tumor should be considered early to prevent irreversible destruction of nervous tissue and unnecessary orthopedic procedures.

The prognosis depends upon the accessibility of the tumor, the histologic type, and the time of operation. Eight of the 13 patients are living but all except two have some residual neurologic deficit.

We wish to express our appreciation to Dr. E. V. Hahn and Dr. C. B. Fausset for permission to use material from their private services and for helpful interest in this paper, and to Dr. J. L. Arbogast, Dr. W. L. Drake, Jr., and Dr. H. M. Banks for use of pathologic material.

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CASE REPORT

Encephalomyelitis in the Preicteric Stage of Infectious Hepatitis

Report of a Case Treated with Aureomycin

M. Streifler, M.D., and S. Feldman, M.D.

INFECTIOUS HEPATITIS is a common virus disease which occurs in both sporadic and epidemic forms. In the orient its incidence is high, and many cases have been observed in the Middle East. While neurologic disturbances in the terminal stages have often been noted, involvement of the nervous system in the preicteric stage seems to be very uncommon. In the reports of Havens[1] and of Barker and his coworkers[2] based on extensive case material, mainly soldiers who served in the Mediterranean theaters of war, no prodromal neurologic complications are mentioned. Leffkowitz[3] observed at least 10,000 patients with infectious hepatitis during epidemics in Palestine, but no neurologic complications were noted.

Since 1940 more than 400 patients have been treated in the Hadassah University Hospital for infectious hepatitis, but the present case is the first to have shown involvement of the nervous system in the preicteric stage. Because of the rarity of the condition and the beneficial effect of Aureomycin on the clinical course, this case is reported.

CASE REPORT

A 19 year old girl was admitted to the hospital with the diagnosis of encephalitis. She was a new immigrant who had arrived from France three months previously. Her medical history was uneventful except for a slight cold from which she had been suffering for three weeks before the present illness began. The evening before admission she had felt warm and dizzy and experienced general malaise. Severe headache and vomiting prevented her from sleeping that night. Next morning she complained of frontal headache, photophobia, and pain when moving the eyes. Examination showed neck stiffness and absent deep reflexes in both legs. Her temperature was 39.6° C. No contagious diseases were reported in the area.

On admission to the hospital the patient was somnolent, kept her eyes closed, and complained of photophobia and severe headache. The presence of definite nuchal rigidity was confirmed; the tendon reflexes were present and equal, but the abdominal reflexes were absent. There was definite weakness in the left arm and a questionable facial weakness of central origin on the left side. The pupils were constricted and reacted sluggishly to light. Examination of the eye

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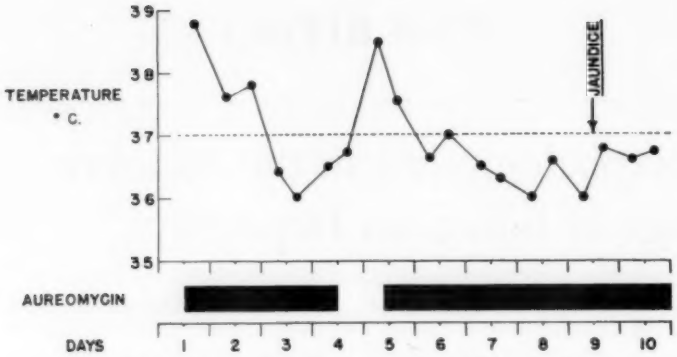

FIG. 1. Temperature changes after treatment with Aureomycin.

grounds showed venous engorgement. General physical examination did not reveal any abnormalities. Her temperature was 38.9° C. and pulse 132. The urine was normal; erythrocyte sedimentation rate was 22/49 (Westergreen); blood sugar and urea were normal. The white count showed 4,300 leukocytes, with 48 per cent neutrophils, 40 per cent lymphocytes, and 12 per cent monocytes. A lumbar puncture revealed a clear fluid under normal pressure and of normal content. The electroencephalographic examination showed a slight generalized disturbance of brain activity. The patient was unable to pass urine spontaneously and had to be catheterized for the next five days.

A diagnosis of encephalomyelitis with meningeal irritation was made, and treatment with Aureomycin, 2 gm. daily, was started (figure 1). The next day a definite improvement was noted; the temperature fell to 37.6° C. in the morning and was 37.8° C. in the evening. The headaches, photophobia, and nuchal rigidity had diminished markedly; abdominal reflexes could be elicited, but there was still weakness in the left arm. The patient complained of nausea and vomited occasionally. On the second night after admission she had an attack of severe headache and dizziness, and on examination showed marked weakness of the left arm, with diminished reflexes. During the next two days her condition improved and she had no fever; because nausea persisted, Aureomycin was discontinued.

Next morning, however, her temperature rose to 38.5° C. and she again complained of severe headache and pains in the back. Neck rigidity and a positive Kernig's sign were found as well as weakness of the left arm and the right leg. In view of the meningeal signs, a spinal puncture was carried out. It revealed a clear fluid, under normal pressure, containing 10 white cells per cu. mm. Treatment with Aureomycin was resumed, and on the following day her temperature again dropped to normal; the patient stated that she felt much better. There was marked regression of the meningeal signs, and, for the first time, she was able to urinate spontaneously.

On the ninth day of hospitalization her skin and sclera became jaundiced and one plus bilirubin was found in the urine. During the next few days blood examinations gave the following results: bilirubin 7.84 mg. per cent; total protein 8.5 gm., albumin 3.9 gm. and globulin 4.6 gm. per 100 cc.; alkaline phosphatase 8.9 units; thymol turbidity 14.5; thymol flocculation ++; cephalin +. The agglutination reaction for Malta fever, Weil-Felix and the heterophile antibody reactions were negative, as well as the Wassermann and Kahn tests. Agglutinations with five strains of Leptospira were negative. Microscopic examination of the blood did not reveal plasmodia or spirochetes.

With the appearance of jaundice, the patient's condition improved. She felt well except for a certain amount of nausea. Aureomycin was stopped and she was put on a diet rich in protein and carbohydrates; vitamin B complex and intravenous glucose were also administered. The jaundice was very slight (only once was two plus bilirubin found in the urine) and began to regress by the sixth day. Repeated neurologic examinations revealed absence of ab-

dominal reflexes and weakness of the left arm.

On the eighteenth day of hospitalization the patient complained of severe vertigo and headache. She stated that for seconds she could not see objects clearly, and that when she tried to change her position in bed the whole room seemed to turn in the same direction. Once, while trying to sit up, she had very severe vertigo and almost fell from bed. Drooping of the right arm was noted in the course of repeated examinations. Aureomycin was again administered and discontinued after a period of five days when these disturbances had disappeared.

The further clinical course was uneventful, and the patient was discharged in good condition after a stay of 35 days in the hospital. When she was examined before discharge, it was found that the abdominal reflexes were markedly diminished and that slight paresis of the left arm persisted. Examination carried out a month later was entirely negative.

COMMENT AND DISCUSSION

This patient suffered from a febrile disease, with involvement of the central nervous system and the liver. Leptospirosis can be excluded on the basis of the clinical picture and the negative agglutination tests. Infectious mononucleosis can also be ruled out since the spleen and lymph nodes were not enlarged, repeated blood counts did not reveal the presence of pathognomonic cells, and four consecutive heterophile antibody reaction tests performed during hospitalization were also negative. Although involvement of the nervous system and of the liver in infectious mononucleosis is not uncommon, their combined appearance seems to be very rare.[4]

The presence of neurologic signs in the preicteric stage of infectious hepatitis is rare. A search of the literature shows that they include meningeal, encephalitic, neuritic, and myelitic involvement. Leibowitz and Gorman,[5] in a recent review, collected 1,365 cases of infectious hepatitis. A meningeal reaction was noted in only one patient, a 10 year old boy who had fever, headache, dizziness, photophobia, and a stiff neck for 48 hours. Jaundice appeared seven days after the onset of illness. No lumbar puncture was reported in this case.[6] Altogether, 15 cases of meningitis associated with infectious hepatitis have been reported, and in all but one the neurologic signs were noted early in the illness, before the onset of jaundice.[5] Examinations of the cerebrospinal fluid in the patient reported here were negative apart from the presence of 10 white cells at one time.

Some cases with encephalitis in the preicteric stage have been reported. Cameron[7] reported temporary paresis of accommodation in two cases out of 120 suffering from infectious hepatitis. Convulsions and hemiplegia were noted in one patient by Brain,[8] while unilateral paresis of the seventh and eleventh cranial nerves were noted in another case.[9] Polyneuritic and myelitic changes are the rarest; few cases have been reported.[10]

The preicteric neurologic complications in the present patient consisted of severe frontal headaches, photophobia, nuchal rigidity, back pain, vomiting, motor weakness, disturbed reflexes, urinary retention, and electroencephalographic changes. These signs and symptoms point toward the presence of encephalomyelitis accompanied by marked meningeal irritation. The presence of otolytic vertigo at the end of the illness deserves mention. To our knowledge, this complication has not been noted previously. Deafness, however, has been reported in a patient on the twentieth day of illness.[9]

A search of the literature reveals that none of the patients suffering from neurologic complications in the preicteric stage of infectious hepatitis had been treated with Aureomycin. Investigation into the effect of Aureomycin on infectious hepatitis has shown that there is no appreciable difference in the clinical or laboratory response between treated and control groups.[11,12] It should be

stressed, however, that the antibiotic was administered to these patients in the icteric stage, when considerable liver damage had already been done. Therefore, it is difficult to draw any conclusions from these cases as to the effect of Aureomycin on the virus of infectious hepatitis.

In the present case, the course of illness in the preicteric stage seems to have been influenced by Aureomycin. Within 48 hours of commencement of treatment the temperature dropped to normal and there was regression of the neurologic signs. When the antibiotic was stopped, there was a return of fever and of neurologic signs, which again disappeared 24 hours after the resumption of antibiotic treatment. No further rises in temperature were recorded during the period of hospitalization. There is room for conjecture as to the relationship between the administration of Aureomycin and the light clinical course of the jaundice.

Two theories have been put forth to explain the neurologic complications in infectious hepatitis.[13] The toxic theory postulates that toxins which come from the intestine (and are not detoxified in the diseased liver) or from destroyed hepatic cells affect the nervous system; the other theory suggests that the virus of infectious hepatitis becomes neurotropic and attacks the nervous system. The prompt effect of Aureomycin on central nervous system signs and on the fever would suggest that an infectious rather than a metabolic factor was the cause of the neurologic complications in our patient. Infectious hepatitis is a generalized viral disease with a predilection for the gastrointestinal tract, but under special circumstances it may attack the nervous system and set up neurologic complications.

It has recently been shown that Aureomycin concentrates in considerable quantity in the central nervous system.[14] Its prompt effect on the clinical picture in the case reported was probably the result of its direct action on the virus in the central nervous system.

SUMMARY

Nervous system disturbances in the preicteric stage of infectious hepatitis appear to be very uncommon.

A case is reported of encephalomyelomeningitis complicating the preicteric stage of infectious hepatitis.

The early administration of Aureomycin seems to have had a markedly beneficial effect on neurologic disturbances.

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CASE REPORT

Two Cases of Guillain-Barré Syndrome Treated with Cortisone

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ACTH and cortisone have produced beneficial results in the treatment of the Guillain-Barré syndrome.[1-4] We are reporting two additional patients exhibiting the Guillain-Barré syndrome and who responded favorably to treatment with cortisone.

CASE REPORTS

Case 1.—A 42 year old construction worker was admitted to Wadsworth General Hospital on July 7, 1952. He was in good health until two weeks before admission when he had a mild upper respiratory infection lasting three days. Two days before admission he noticed an intermittent tingling sensation in the soles of both feet. The next morning his legs were weak and he fell repeatedly. He was seen by a physician who gave him an intravenous injection of calcium gluconate. He felt stronger for a few hours, but the weakness in his lower extremities then became more severe. In addition, he noted weakness of the hands and arms. The temperature on admission was 100° F., pulse 84 per minute, respirations 20 per minute, and blood pressure 126 mm. Hg systolic and 82 mm. Hg diastolic. He manifested weakness which was generalized except for those muscles supplied by the cranial nerves. Triceps and biceps reflexes were weak. No reflexes could be obtained over the abdomen or lower extremities. No other abnormal physical signs were observed.

His vital capacity was 2,600 cc., approximately 65 per cent of the anticipated normal. The white blood count was 20,000 with 88 per cent polymorphonuclear cells; red blood count was 5,800,000. The sedimentation rate was 16 mm. per hour. The blood and spinal fluid Wassermann tests were negative. The spinal fluid was under normal pressure, and contained 79 mg. of protein per 100 cc. and 3 lymphocytes per cu. mm. The colloidal gold curve was 0011100000.

The day after admission he exhibited signs of progressive flaccid paralysis. No trace of voluntary muscular activity could be demonstrated in the extremities. All tendon reflexes were absent. In addition, swallowing became difficult and respirations more shallow. The vital capacity fell to 800 cc., and the tidal air to 200 cc. Cyanosis was noted and he became lethargic. Mucus accumulated in the trachea and pharynx and was aspirated continually. He was placed in a tank type respirator and a tracheotomy was performed. He was started on oral cortisone, 250 mg. daily. Within 24 hours the ability to swallow had improved considerably. On the second treatment day, supination of the right forearm and flexion and extension of both great toes were noted. On the third treatment day, swallowing was entirely normal. Active though weak voluntary contractions of the muscles of the abdomen, both thighs, and forearms were observed. A weak patellar tendon reflex on the right reappeared. On the fourth day of cortisone therapy he was able to remain outside

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the respirator for ten minutes. A lumbar puncture on the fifth day showed a total protein of 95 mg. per 100 cc. without increase in cells. Cortisone was reduced to 150 mg. daily after the first six days. For the next two weeks, he complained of steady aching in the back and both legs. Muscular power improved steadily. Within two weeks he was able to breathe unassisted without undue fatigue for two-hour periods several times a day. At the end of four weeks he no longer required a respirator. Cortisone dosage was gradually reduced and discontinued after a total of 30 days. On August 20, 1952, approximately six weeks after admission, he started to walk. The tracheotomy was allowed to close. When he was discharged from the hospital on September 23, 1952, he showed no recognizable respiratory impairment. His vital capacity was 3,500 cc. Slight weakness of the extremities remained, but appeared to be subsiding rapidly.

Case 2.—A 46 year old white grocery clerk was admitted to Wadsworth General Hospital on September 28, 1952. He was in good health until three weeks before admission when he noted pain and clear vesicles on an erythematous base in the left flank. Herpes zoster was diagnosed by his physician who prescribed various medications, including Aureomycin. Two days prior to admission he became nauseated and vomited. This continued until the day of admission. The temperature on admission was 98.6° F., pulse 80 per minute, and blood pressure 170 mm. Hg systolic and 90 mm. Hg diastolic in prone position, and 120 mm. Hg systolic and 80 mm. Hg diastolic in sitting position. Several small crusted vesicular lesions, characteristic of herpes zoster, were noted in a small area in the left lower quadrant of the abdomen. Moderate weakness was noted in both upper extremities and slight weakness in both legs. Physical examination was otherwise entirely normal.

The hemoglobin was 18.3 gm.; the white blood count 14,500 with a normal differential. Urinalysis was normal. The spinal fluid contained 108 mg. of protein per 100 cc. No cells were found. The colloidal gold curve was 0000000000.

Three days after admission he appeared slightly lethargic and had considerable difficulty with respiration and coughing. Muscles supplied by the cranial nerves were intact except for slight weakness of the facial muscles on the left. Superficial reflexes were absent. Deep tendon reflexes were unobtainable except for a greatly decreased biceps tendon reflex on the right. The muscles of all extremities became weaker; the right arm and leg were more severely affected than the left. There was slight decrease in pain perception in both lower extremities. Vibratory sensation in both feet was reduced. All other sensory modalities were intact. On October 1, the vital capacity was 2,200 cc. and on October 3, 1,600 cc. (39 per cent of normal). The spinal fluid protein had risen to 159 mg. per cent. He was given 300 mg. of cortisone intramuscularly. The following day he felt better and several observers noted improved function of the respiratory muscles. He was given 200 mg. of cortisone intramuscularly daily for the next three days. On October 8, the spinal protein was 218 mg. per cent. On the second day of treatment much more vigorous plantar flexion and dorsiflexion of both feet were observed and movements of the upper extremities were more active. His ability to cough was greatly improved so that frequent aspirations of bronchial secretions became unnecessary. The dosage of cortisone was decreased gradually over the next two weeks. Muscular strength increased steadily and in four weeks the patient walked without support. Cortisone was discontinued on October 30, 1952. Five weeks after admission the patient left the hospital. Muscular strength was not entirely normal but continued to improve after discharge.

DISCUSSION

There are a number of reports in the literature describing pathologic findings of the affected tissues in this syndrome. While in the past a large variety of changes have been described by different pathologists, fairly uniform observations have been made more recently. Scheinker[5] examined sections of nerve tissue in ten fatal cases and found consistent changes in all. The axis cylinders in the nerve roots showed diffuse enlargement due to pronounced edema. Some showed various stages of degeneration such as fragmentation and "cork screw" formation. The myelin sheaths showed less obvious changes but they, too, demonstrated irregular swelling and beading. In a number of cases, the spinal cord showed swelling of a minor degree in

some anterior horn cells, and some cell nuclei showed various stages of degeneration. The axis cylinders in the white matter of the spinal cord showed marked swelling. The remarkable finding in all sections was the absence of any inflammatory reaction. Similar descriptions were found in the cases reported by Gilpin, Moersch, and Kernohan[6] and Roseman and Aring.[7]

These microscopic changes are identical to those described in a variety of allergic reactions. The course of events in this syndrome favors the concept that allergy plays a significant role in its etiology. The onset is usually preceded by an infectious process or exposure to drugs. This is followed by a symptom-free interval of one to three weeks, terminating in the paralytic phase. This is similar to the occurrence of glomerulonephritis or rheumatic carditis following streptococcal infection.

The occurrence of flaccid paralysis of the striated muscles might therefore be explained as follows: The nerve roots leave the spinal canal through fairly rigid openings in the meningeal membranes. Thus, there is a limit to the degree of edematous swelling at that site. If the edema continues to increase, compression of the axis cylinders with subsequent loss of function will result. The extent of the paralysis may depend on the duration and severity of the edema. Those nerve fibers which have sustained the least damage can be expected to recover sooner when the edema begins to subside. The use of adrenal corticoids in an effort to inhibit allergic edema seems to be rational, and, thus, it would be advisable to institute treatment as early as possible.

The Guillain-Barré syndrome has been reported as a complication of metastatic carcinoma of the meninges and of widespread arthritis of the spine. In these diseases there is actual compression of the nerve roots by extraneous disease rather than swelling of the axis cylinders. Irreversible compression and destruction of the nerve roots occur, and cortisone would not be expected to be beneficial.

A number of papers[8–18] have been reviewed to compare the duration of the syndrome under various methods of treatment. It was found very difficult to evaluate the effectiveness of these therapeutic measures since an extreme variability exists in the recovery period even of the untreated case. It was noted that mild cases can show pronounced improvement within one week. The severe cases, particularly those with paralysis of the respiratory muscles, had a very much longer period of morbidity ranging from six months to three years and averaging from six months to one year.

The case described by Seltzer and his coworkers showed severe involvement of the cranial, bulbar, and spinal nerves. Twenty-four hours after institution of ACTH, objective improvement was noted and recovery was nearly complete within four weeks. The case of Stillman and Ganong[2] manifested very similar findings. The first signs of improvement appeared within six hours after ACTH was administered, and he was discharged nearly well six weeks later. The case of Newey and Lubin[3] demonstrated almost instantaneous improvement with intravenous administration of ACTH. However, a relapse occurred after ten weeks and retreatment again resulted in immediate improvement. The case described by Blood and his coworkers,[4] which was very severe, responded within 24 hours to ACTH given intravenously. This patient also suffered a relapse upon discontinuation of therapy, but prompt improvement followed reinstitution of therapy with ACTH. The latter two cases were treated initially with ACTH for less than two weeks, which may be too short a period. After four to eight weeks of therapy for the relapses, improvement continued without interruption.

Our two cases followed a similar pattern of recovery. Case 1, manifesting a complete paralysis of all striated muscles of trunk and extremities, recovered in two months. Case 2 was discharged from the hospital almost well in five weeks. Both cases manifested signs of return of muscular function within the first 24 hours after institution of cortisone. It is recognized that the apparent surprising improvement in only six cases cannot be considered as final proof of the value of ACTH or cortisone therapy in this syndrome. However, the uniform improvement within the first day of treatment and the short recovery periods suggest a specific action of ACTH and cortisone.

SUMMARY

Two cases of Guillain-Barré syndrome with severe muscular paralysis are presented. Both were treated with cortisone within one week after onset of symptoms. No adverse side effects were observed. Some improvement was noted within 24 hours after treatment was instituted. Case reports in the literature do not report this phenomenon in patients treated without cortisone. Recovery was nearly complete in one and two months, respectively. These recovery periods were shorter than those reported in the literature in cases of similar severity. Cortisone should be given further clinical trial.

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Neurology BOOK REVIEWS

The Neurophysiological Basis of Mind.
The Principles of Neurophysiology.

J. C. Eccles. 1953. New York: The Oxford University Press. 314 pages. $6.50.

This book, by the professor of physiology in the Australian National University at Canberra, is an amplification of the Waynflete Lectures delivered by the author in 1952 at Magdalen College, Oxford. For the most part the book is a presentation of the principles of neurophysiology, and especially the more recent work done on the nature of the nerve impulse, its electrical properties, the mechanisms of neuromuscular and synaptic transmission, and the role of feed-back mechanisms and circular circuits in cortical function. Considerable emphasis is laid upon the work of the author and his group in the Dunedin laboratory upon the nature of the synapse and its mechanisms. As a unified presentation of this work the book has considerable value. In the end the author's metaphysical interests become evident in his espousal of Cartesian dualism and interactionism as a solution of the mind-matter problem.

The ionic hypothesis as to the nature of the nerve impulse is succinctly presented, with a helpful discussion of the experimental bases for the theory. The resting membrane of the nerve fiber, readily permeable to K and Cl ions, is sparingly permeable to Na ions, and an active "sodium-pump" mechanism, located in the membrane and driven by metabolic energy, removes Na ions from the interior as fast as they diffuse in, so that they have only 0.1 the concentration within the fiber as without. This unequal distribution of Na ions, and a concentration within the fiber of impermeable anions – chiefly glutamic and aspartic acid – result in an unequal distribution of K and Cl ions, the concentration of internal K being 20 to 50 times that of the external, while the reverse proportions exist for Cl. Consequent upon these ionic distributions, the outside of the membrane is 75 to 100 millivolts positive to the inside. When an electrical stimulus is applied outside the membrane artificially, or by the flow of electric currents in local circuits incident to the passage of a nerve impulse, the "depolarization" which results draws Na ions into the fiber along the steep electrochemical gradient. Eventually the interior becomes positive to the outside, a condition which leads to a rapid net outflow of K ions. Thus, the original resting potential is rapidly restored. But these changes in potential cause currents to flow which depolarize successively one region of the fiber after another, indefinitely. After the

passage of the impulse in this fashion, the original unequal concentrations of ions are more slowly restored by the activity of the "sodium pump," thus leaving the fiber ready for another impulse.

In myelinated nerve fibers ionic exchange occurs only at the nodes of Renviér, while the internodal areas have so low a capacity that less than 1 per cent of ionic exchange is necessary as compared with nonmedullated fibers. The gain in efficiency is enormous.

The author accepts the chemical (acetylcholine) hypothesis for transmission of the impulse at the motor end plate. At the synapse he also believes a chemical transmission operates, since the action currents of the pre-synaptic impulse are probably inadequate to induce the large ionic flux that is required for the post-synaptic potential. Furthermore, generation of a post-synaptic impulse requires the summation of many unitary post-synaptic potentials to give the critical level of depolarization.

Considerable attention is devoted to the electrical events accompanying inhibition, for example, that seen in antagonists of a synergic movement. He concludes that inhibition results from a hyperpolarization of the surface membrane of the motor neurone, so that the post-synaptic potential necessary to generate an impulse becomes unattainable by the presynaptic impulses. This hyperpolarization he considers the result of the liberation of a specific substance by "inhibitory synaptic knobs." He thus believes that inhibition is accomplished by special inhibitory fibers ending in inhibitory knobs. Further, synergy results from excitation of some motor neurones (agonists) and inhibition of others (antagonists) by anatomically distinct fibers and synaptic knobs, an effect which must depend upon the "grouping together" of appropriate motor neurones belonging to synergic muscles. Clearly, this implies that synergy is inborn – a thesis scarcely acceptable in view of the necessity of learning synergy in early life. In general, the author thinks that reflex synergy depends upon "elaborate interlocking servomechanisms" to govern reciprocal innervation.

"Information" is transmitted in the nervous system by code messages of varying frequency. Post-synaptic potentials are built up by spatial as well as by temporal summation of incoming impulses of these varying frequencies. Inhibition similarly results from summation of inhibitory impulses.

The problem of the mechanisms of learning and memory attracts much of the author's attention. To this problem he has devoted much original work. Briefly, and without recounting his experimental evidence, it is his hypothesis that learning occurs at central synapses, since the passage of impulses across synapses is facilitated by repetitive use of the synapse. He conceives this facilitation as resulting from a swelling of tetanized presynaptic nerve fibers and synaptic knobs, resulting in closer anatomical union of the elements at the synapse. He thus arrives at a structural basis for memory in plastic changes at synapses.

In a stimulating discussion of the electrical activity of the cerebral cortex, the author arrives at the conception that spontaneous cortical (alpha) rhythms observed in the electroencephalogram are due to closed circuits of neuronal activity rather than to inherent rhythms of the neurones, that normal cortical rhythm depends upon continuous inflow of impulses from the thalamus, while strong sensory inflow breaks up the alpha rhythm into fine, rapid irregular waves, and that delta waves of injury or sleep may be partly caused by impulses of cortical neurones or, perhaps more likely, by inflow from subcortical centers. He insists that more accurate knowledge of

cortical function awaits intracellular study of pyramidal cells by microelectrodes, and better knowledge of synaptic transmitter mechanisms. He assumes these transmitter mechanisms utilize acetylcholine.

In his last chapter the author speculates on the possible manner in which the "power of will" may influence the neuronal processes and so exemplify the interactionism of the Cartesian dualism of mind and matter. In a word, he supposes that the cortex which, in consciousness, is in a state of extreme sensitivity as a detector of minute spatiotemporal fields of influence, may be influenced by the mind in willed action upon microscopic patterns of neuronal activity at their synaptic connections. He seems to hold that such action of the mind on the functioning brain is more plausible since it need produce only the most miniscule changes to sway the patterns of activity. He ends with an appraisal of his own work as a "fairly adequate functional description of the nervous system that is based on physics and chemistry and that gives some clue as to the manner in which the gulf between mind and matter may ultimately be bridged."

It is difficult to appraise this book. In the first place, it is an instructive and useful summary of the most recent work on the intimate electrophysiology of the neurone and the synapse, and a stimulating discussion of the function of neuronal networks. It is, further, an excellent guide to the work of others in the field, and to the contributions of the author and his group at the Dunedin laboratory on the nature of the nerve impulse and the mechanisms at the synapse. The bibliography is most helpful. Clearly written, the book, because of the subject, is difficult reading for the uninitiated.

For a reviewer not working in the field, criticism is presumptuous. Yet certain impressions come strongly to mind. Some of the author's concepts seem naive and admittedly need objective verification. To base plasticity of the nervous system and the processes of learning and memory upon structural changes at the synapse in the form of a sort of water-logged swelling of the synaptic knobs through repeated stimulation is an example. This is merely synaptic facilitation as an explanation of the old engram-concept of neural "grooves," a theory not too consistent with the facts now available. The specificity of the psychologic concept and the processes of recall and recognition in memory can scarcely depend on anatomical pathways, but rather upon specific spatial and temporal patterns of activity in *varying* groups of neurones. It is the mode of *activity* which must be specific, not the neurones mediating the activity. Nevertheless, one may readily confess that these specific patterns of activity must somehow achieve facilities upon their passages through the neuronal network.

It seems, further, that the theory that inhibition and excitation utilize anatomically-separate nerve fibers with specific and opposite transmitter substances at the synapse must need confirmation. Synergy, it would seem, must be learned; it is not laid down in the nervous system *ab origine*. If this is true, it would appear necessary to assume the establishment of inhibitory and excitatory functions in nerve fibers appropriated for that purpose. Furthermore, hyperpolarization of the neurone would seem an inadequate mechanism, since it can impose only inactivity upon the neurone, while inhibition seems often to be an active process rather than absence of activity.

Despite these criticisms, this work is useful and instructive as a review of neurophysiology in its basic principles, and as an introduction to the fantastic processes of neuronal function.

R. P. M.

The Living Brain.

W. Grey Walter, M.D. 1953. New York: W. W. Norton and Company. 311 pages, $3.95.

This book records the impact upon a very philosophic author of the extremely fruitful method of electroencephalography in the study of the living brain. The book is directed to the general reader.

In his explanations of phenomena, the author adopts an evolutionary theory. In his graphic descriptions of how things came to be from the "original stardust," he reaches such great flights of fancy that he comes perilously close to that borderland where, pushing the evolutionary hypothesis too far, a proponent shades into absurdity. However, the literary quality is delightful and compels the reader's attention.

Important emphasis is placed on arguments for workers to continue on fundamental problems in the field of electroencephalography and not to be entirely distracted by its clinical applications. The author is interested in fine technics, in careful measurements, in the summing up of frequencies by the frequency analyzer, and the projection on a suitable screen (toposcope) of the electrical activity of a hemisphere of the brain using radar methods. Utilizing these procedures, the author details his studies on the electrical patterns characteristic of personality types and various states of consciousness. Thus, he finds that alpha rhythm is a scanning, a process of reaching for a pattern, that is, mentally searching for a word. When this is found, it becomes the object of attention, and alpha rhythm gives way to a low voltage fast pattern. This analysis of function and constant seeking for finer and more delicate technics lends itself to emphasizing the basic role of the morphologic units in any explanation. It is natural, then, that the work of W. Grey Walter gives an immense impetus to the study of neuroanatomy. The dynamic concept of structure leads straight back to the exquisitely detailed discoveries of the fine interconnections of neurones – to the "textura del sistema nervioso" by Ramon y Cajal and those who followed his path. At the present time, some of the most important and basic neuroanatomic research is coming from electroencephalographically-oriented investigators.

Most of the readers will be fascinated by the detailed descriptions of elemental robots referred to as toys by the author, which reproduce many of the characteristics of the nervous system of the living animal. The names of these toys and their general functions are: *machina sopora* or "homostat" designed by Ashley which, by utilizing various radio tubes, will select out of 360,000 possible connections, one which leads to a condition of dynamic internal stability; *machina speculatrix* which incorporates devices for "goal seeking" and "scanning;" *machina docilis* which can be taught to come at the sound of a whistle; and *machina labyrinthia* which is goal-seeking, self-regulating, and finds its way out of a maze.

This book is recommended to all those interested in the neurologic sciences and in particular to those philosophically inclined. Passage after passage in the book invites disputation and stimulates the intellect of the reader. A knowledge of electroencephalography is not necessary in order to follow the author's discussion. It is true that this work emphasizes the role of electroencephalography in clinical and basic neurology, but to this the reviewer finds no objection.

A. B. V.

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